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# CLINICAL EMERGENCIES

## ARTICLES


| | | |
|---|---|---|
| Ostetrical Emergencies | *J. C. Billinghurst* | 5 |
| Salicylate Poisoning in Children | *M. F. Smith* | 11 |
| Diagnosis and Treatment of Pulmonary Embolism | *E. L. Book* | 16 |
| Hyperglycaemic Hyperosmolar Nonketotic Coma | *May Ho* | 20 |


## FEATURES


| | | |
|---|---|---|
| Clinicopathological Conference | *J. Wolcholk* | 24 |
| Multiple Round Quiz | *H. P. Drutz, M.D.*<br>*F. G. Sommers, M.D.* | 26 |

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HOMEWOOD SANITARIUM ..... 15

ONTARIO CANCER INSTITUTE ..... 1

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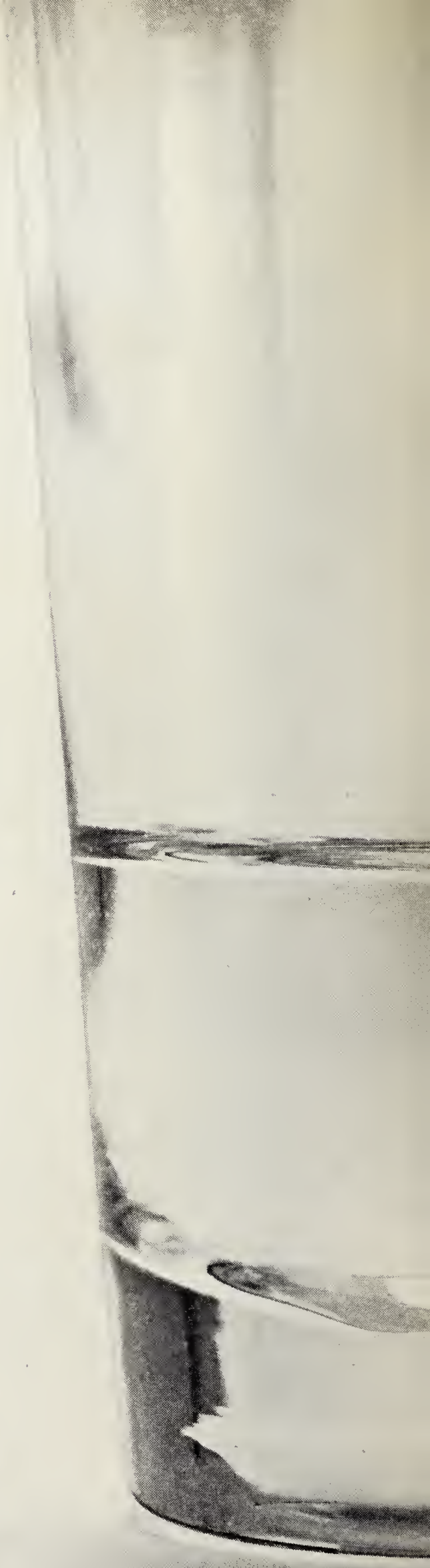

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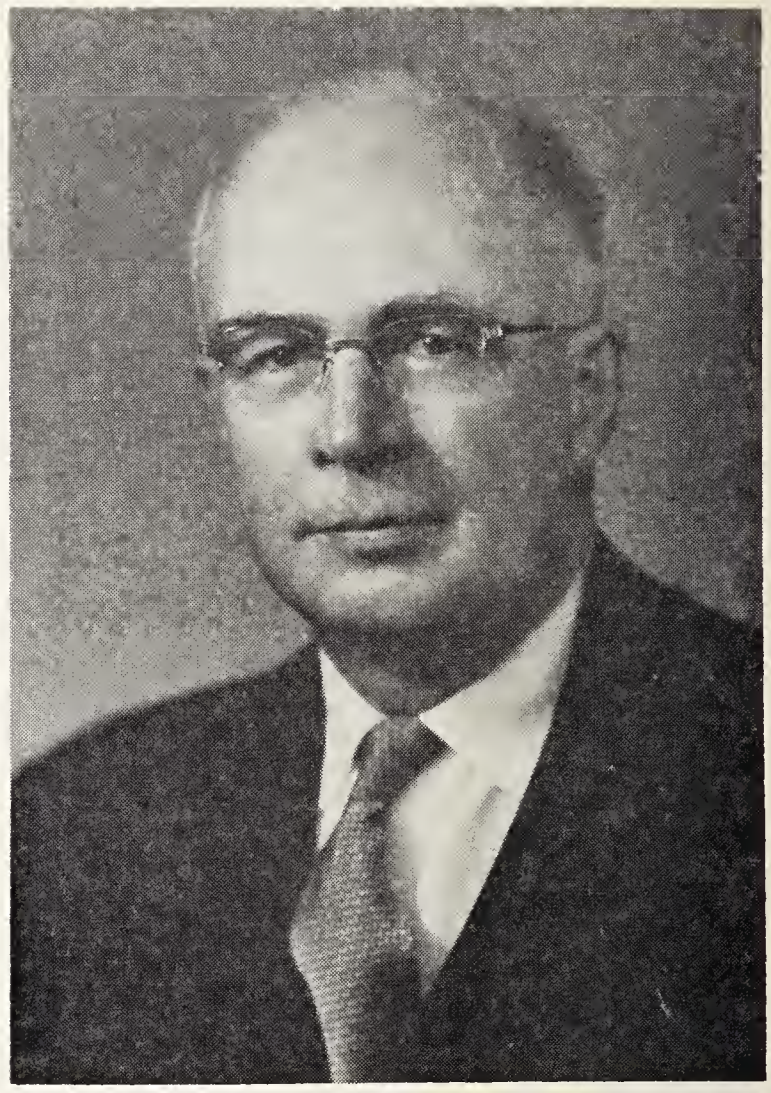
# GUEST EDITORIAL

*Dr. Gordon was born on Aug. 2, 1911 in Watrous, Sask. where he attended high school. With a B.Sc. (Sask.) 1934 and M.D. (Toronto) 1937, he interned at the Toronto Psychiatric Hospital and the Toronto General Hospital where he took his residency in 1938-39. He received certification of the conjoint board of the Royal Colleges of Physicians and Surgeons, England, in 1940 and has held the F.R.C.P.(C) since 1952. He held various positions in the Royal Canadian Army Medical Corps from 1939 to 1945, then joined the active teaching staff of the U of T.*

*He is at present Professor and Head, Dept. of Anaesthesia, U of T and Anaesthetist-in-chief, TGH, as well as consultant in Anaesthesia to the University of Toronto teaching hospitals.*

*Dr. Gordon is the recipient of several honours including the Centennial Medal in 1967. He is the editor of* Canadian Anaesthetists' Society Journal *and the author of about sixty articles and monograms. His hobbies include music (he is a violinist), cabinet making and pampering his summer cottage in Georgian Bay.*



## *Clinical Emergency*

A CLINICAL EMERGENCY may be defined as a situation which will result in death of the patient or serious morbidity, unless appropriate treatment is applied promptly. The important words here are *appropriate* and *prompt.*

The prompt institution of treatment depends, of course, on recognition that an emergency exists. In some instances the problem may be so obvious as to be evident to a lay observer, while in others the recognition that emergency treatment is necessary may require sophisticated and special knowledge and a modicum of clinical experience.

The emergency situation may be precipitated by some cataclysmic event, or it may be the result of a more slowly evolving process resulting from the patient's disease or his treatment. Early recognition of the process in the more slowly evolving situation may reduce the urgency of management and allow more time for the orderly definition and correction of precipitating causes. Such early recognition of the potentially lethal process relies on a reasonable index of suspicion and informed intelligent observation of the patient. The value of early recognition depends on doing something about it!

Collapse of function of the cardio-respiratory mechanism, with failure of perfusion and anoxia of vital organs is the end-result in all circumstances which may be classified as clinical emergencies. When the situation has deteriorated to this point, the appropriate and essential treatment is prompt re-establishment of adequate levels of ventilation and circulation. Only when this has been done is there time for elucidation and treatment of the basic cause of the disaster. *Ventilate, don't vaccilate* and remember that *oxygen is good!*

R. A. GORDON, M.D., F.R.C.P.(C)
Professor and Chairman,
University of Toronto Department of Anaesthesia.

# REPRODUCTION

# *Obstetrical Emergencies:*

*J. C. Billinghurst, 7T1*

## *1. Third Trimester Bleeding* *2. Fetal Distress*

### INTRODUCTION

Obstetrics is a unique branch of medicine, in that when dealing with obstetrical emergencies, not only the fate of the fetus, but also that of the mother may be at stake. Although there are many situations in obstetrics that might be termed emergencies, two of the most important ones, third trimester haemorrhage and fetal distress, are chosen for discussion in this paper. In the face of the large volume of literature that has been written on these topics this paper attempts to present the significant points of each topic, as well as review some of the more recent work, where applicable.

### I. THIRD TRIMESTER HAEMORRHAGE

ETIOLOGY – Most of the likely causes of third trimester haemorrhage can be divided into two main groups:

1. *Conditions caused by pregnancy*
   (a) idiopathic causes – probably marginal sinus rupture
   (b) placenta praevia
   (c) abruptio placentae
   (d) uterine rupture
   (e) vasa praevia
   (f) show
2. *Conditions not caused by pregnancy*
   (a) cervical polyps
   (b) cervical erosion
   (c) inflammation – vulvitis, cervicitis
   (d) carcinoma of cervix
   (e) bleeding diathesis
   (f) vaginal varices
   (g) urinary tract infection
   (h) hemorrhoids

While the above outline is a useful guide in assessing third trimester haemorrhage, it is not the purpose of this paper to deal with each of these causes in detail. Rather, only the first group will be discussed.

INCIDENCE – The commonest cause of any third trimester bleeding is "show". This is the discharge from the vagina of a small amount of blood-tinged mucous which represents the mucous plug that fills the cervical canal during pregnancy. Any substantial bleeding greater than this suggests pathology.

Placenta praevia, abruptio placentae and idiopathic causes together account for bleeding in about 3% of all births, with idiopathic causes accounting for about half of this figure. The incidence of placenta praevia approximates 0.5% of pregnancies, while that of abruptio placentae is about 1%. These figures vary somewhat from study to study.

Rupture of the uterus occurs in about 0.1% of North American births, and is usually associated with external haemorrhage, which may be slight. Bleeding due to vasa praevia is even less common.[1]

PATHOGENESIS – A brief discription of each of the causes, other than "show", is now presented.

(1) *Placenta praevia* – Here, the placenta is implanted low in the uterus where it totally or partially overlies the internal os, or just reaches the margin of the os. As the os dilates during labour, the placenta covers more and more of it. Because of the separation of placenta from underlying decidua, bleeding from the ruptured vessels occurs. The cause of placenta praevia is unknown, but multiparity and increasing age favours its occurrence. It is interesting to note that placenta praevia recurs in 6% of pregnancies following an earlier placenta praevia.

(2) *Abruptio placentae* – Premature separation of the normally implanted placenta occurs in abruptio placentae. Separation may occur at the margin of the placenta, leading to external haemorrhage (80% of cases), or less commonly, centrally, in which case bleeding is concealed (20%). A variety of causes have been suspected, but the primary cause of abruptio is unknown. Trauma is demonstrable in less than 5% of cases.

(3) *Idiopathic causes* – Although, by definition, the exact cause for bleeding in these cases is unknown, many are suspected to result from marginal sinus rupture. Since this is, in effect, a form of abruptio placentae, idiopathic causes will not be further discussed in this article.

(4) *Rupture of uterus* – This serious accident may occur in 3 ways: rupture of a previous uterine scar, spontaneous rupture of an intact uterus, and traumatic rupture of an intact uterus. Classical Caesarian section scars more commonly (3-4 times) rupture than lower segment scars. Spontaneous rupture occurs more commonly with increasing parity and age, and is often associated with cephalopelvic disproportion. Traumatic rupture may result from external trauma, such as a blow to the abdomen, or internal trauma, as in version procedures.[1]

(5) *Vasa praevia* – Naftolin states that vasa praevia exists when velamentous insertion of umbilical vessels

and the vessels within the amnion are located in front of the presenting part. Effacement of the cervix or descent of the fetal presenting part may result in rupture and/or occlusion of these vessels. He notes that velamentous insertion occurs in about 1% of normal uncomplicated gestations but in about 10% of multiple pregnancies.[2]

PRESENTATION – At this point, a summary of the important clinical features of each of these conditions is given.

(1) *Placenta praevia* – Here, painless hemorrhage occurs suddenly without warning, but usually stops spontaneously. The uterus is soft and non-tender. The fetal heart is audible on auscultation. The presenting part is not in the pelvis unless a partial or marginal placenta praevia exists, which may allow some descent. Abnormal presentations are frequently seen, i.e. breech in 16% and shoulder in 9%.

(2) *Abruptio placentae* – External hemorrhage is seen in 80% of these cases (concealed in 20%). A rigid, tender uterus is an important differentiating finding. There may be persistent pain, and the tenderness may be generalized, or localized to the site of abruption. The presenting part may or may not be in the pelvis. Typically, fetal heart sounds are absent, or if they are audible, there is distress (see Fetal Distress).

(3) *Uterine rupture* – Spontaneous and low segment scar ruptures rarely occur before labour, while one-third of classical Caesarian scar ruptures do so. Rupture may extend into the abdominal cavity or be separated from it by the peritoneum of the uterus and its adnexa.

The first clinical indication of rupture is a sudden, sharp, shooting abdominal pain experienced by the mother. The pain ceases and hemorrhage is seen. The uterus is tender, but is small and has no contractions. The fetus may be palpable beside the uterus. Foetal heart sounds are not present, indicaitng fetal distress.

(4) *Vasa praevia* – This rarely diagnosed situation is characterized by hemorrhage seen simultaneously with membrane rupture. There is no pain and the uterus is non-tender. There may be an abnormal presentation. The fetal heart is in distress or is silent.

PROGNOSIS – Placenta praevia has a maternal death rate of only about 0.1%, while abruptio has a similarly low rate (less than 1%). Rupture of a Caesarian section scar has a 5% rate while spontaneous and traumatic rupture are associated with a 4-8 times increase in maternal death rate[1].

As far as perinatal mortality is concerned, vasa praevia has a rate close to 100%[2], rupture has one of 50-75%, abruption kills about 50% of its fetuses,[1] and placenta praevia is associated with a 10-25% perinatal mortality.[3]

## DIAGNOSIS

(1) History and physical examination are the most important diagnostic tools.
(2) No vaginal or rectal examination should be done in a third trimester bleeder unless the patient is in a delivery room set up for vaginal or abdominal delivery (double setup). Such an examination is unwise unless delivery in the near future is contemplated since fatal bleeding may result.[1]
(3) Conditions not associated with pregnancy should be ruled out.
(4) Clotting defects should be ruled out.
(5) Radiologic studies may be helpful. These include soft tissue techniques, placenta scan, and, rarely, angiography.
(6) Ultra-sound technique may be useful (see Fetal Distress).
(7) Hormone and enzyme tests may also be employed (see Fetal Distress).

## TREATMENT

(A) *General Treatment*

(1) No rectal or vaginal examination should be done.
(2) No vaginal packing should be used. It is useless in stopping bleeding and may cause more bleeding or introduce infection.[1]
(3) The patient should be admitted to hospital immediately. A third trimester bleeding patient should never be sent home.
(4) The patient's blood should be typed and cross-matched for an appropriate number of units for transfusion.
(5) It is imperative to monitor vital signs of the mother and the fetal heart as closely as the situation indicates.
(6) Intravenous fluids and/or blood to replace volume losses are started immediately.
(7) The patient is kept on complete bed rest until bleeding has stopped.
(8) Nothing is given by mouth to the patient if there is a possibility of delivery in the next few hours.

(B) *Specific Treatment*

When deciding if treatment in a particular case should be one of expectancy or of delivery, a number of factors must be considered. Some of these include the severity of bleeding, whether the mother is in labour or not, the period of gestation, fetal status, whether the membranes are intact, and the presence of complications. Obviously, all the possible combinations cannot be discussed, but a few general guidelines are presented.

(1) PLACENTA PRAEVIA

(a) *Expectant treatment:* This form of treatment is designed to allow the fetus more intrauterine time which will minimize the high neonatal mortality associated with prematurity. For example, if bleeding has stopped,

the membranes are intact, the patient is not in labour, and a living fetus of less than 36-37 weeks gestation is present, the patient can be carefully watched in hospital.

(b) *Delivery:* If severe bleeding or significant fetal distress is present, delivery must be considered. Vaginal delivery is sometimes used in multiparas with low placental implantation so that the fetal head drops down to compress the placenta and control bleeding. In all primiparas and most other cases of placenta praevia, Caesarian section is the accepted method of treatment. It allows for a quick delivery and rapid control of bleeding, and prevents cervical or low segment lacerations.[1]

(2) Abruptio Placentae

(a) *Expectant treatment* – With abruption, expectant therapy is not used.

(b) *Delivery* – The usual treatment of abruption is delivery, preferably within 6 hours of the diagnosis. Artificial rupture of the membranes plus oxytocin stimulation are followed by Caesarian section if no effective labour that will produce delivery within 6 hours is imminent. Hysterectomy for severe Couvelaire uterus may be necessary.[1]

Treatment of hypofibrinogenemia and acute renal failure may be required.

(3) Uterine Rupture

(a) *Prevention* – Caution must be observed to avoid situations that may lead to rupture, for example overstimulation of the uterus when cephalopelvic disproportion is present.

(b) *Laparotomy* – Regardless of fetal status, laparotomy is the only treatment for uterine rupture. Once the fetus is removed, the uterus and adnexa may be repaired or hysterectomy may be performed.[1]

(4) *Vasa praevia* – When this diagnosis is made, prompt delivery is required, for fetal mortality is very high. The use of the vaginal route is accepted if delivery is possible quickly. Abdominal delivery may be necessary with abnormal presentations.

## II. FETAL DISTRESS

Definition – No universally acceptable definition of fetal distress exists at present, partly because of the disagreement over the significance of various signs of fetal compromise. Davis states that fetal distress refers to any condition of the fetus or mother associated with an increased probability of fetal death or morbidity.[4] Hon simply defines it as a condition in which fetal well-being is jeopardized.[5]

Incidence – Few writers have commented on the general incidence of fetal distress, but one study estimates that it occurs in about 4% of all labours.[6]

Etiology – There is a large number of possible causes of fetal distress that can be divided into four main groups.

(1) *Infant* –

- (a) Prematurity
- (b) Congenital malformations
- (c) Erythroblastosis
- (d) Toxic and drug-induced effect.

(2) *Umbilical cord* – Any condition which embarrasses the circulation of the cord may lead to fetal hypoxia.

- (a) Prolapse of cord
- (b) True knots
- (c) Looping of cord around neck or limb
- (d) Vasa praevia

(3) *Placenta* – Premature separation of the placenta, if extensive enough (50% or more) will cause fetal distress.[6]

- (a) Placenta praevia
- (b) Abruptio placentae
- (c) Marginal sinus rupture
- (d) Uterine rupture

(4) *Mother* –

- (a) Maternal hypotension
  - (i) supine hypotensive syndrome
  - (ii) post-hemorrhagic
  - (iii) spinal anaesthesia
- (b) Dysfunctional labour
  - (i) cephalopelvic disproportion
  - (ii) hypertonic uterus
- (c) Diabetes
- (d) Toxaemia
- (e) Chronic hypertension
- (f) Chronic renal disease
- (g) Cardiac disease
- (h) Other systemic diseases – infection
  – anemia

### DIAGNOSIS OF FETAL DISTRESS

(A) History – The first step in diagnosis of fetal distress is the taking of a relevant medical history as well as an obstetrical one. One tries to discover a high risk pregnancy; in other words, a pregnancy during which fetal distress is very likely to occur. The obstetrician wants to become aware of such maternal problems as diabetes, renal disease, cardiac disease and the other maternal causes of fetal distress which might lead to fetal compromise. Similarly, an obstetrical history is important in allowing one to be prepared for the recurrence of previous problems or sometimes the occurrence of new ones.

A change in fetal movements as noticed by the mother may be of limited significance. Such sensations are often incorrectly reported by an over-anxious mother, hence the personality of the mother plays a large part in this symptom. Fetal movements, whether increased or decreased, are usually of limited diagnostic value.

(B) Physical Examination

The most important and most commonly used indices of fetal distress are changes in fetal heart rate or rhythm. These are usually detected by auscultation, but may also be detected by fetal EKG or by ultra-sound techniques. There are three main types of changes which may occur singly or in combination.

(a) *Bradycardia* – Although the fetal heart rate may normally fall as low as 110-120 beats per minute between contractions, fetal bradycardia (less than 100 beats per minute during contractions) may indicate fetal distress. Hon has studied fetal bradycardia using simultaneous measurement of amniotic fluid pressures, and he speaks of three different patterns of fetal heart "deceleration".

The first type is "early deceleration" which begins with an uterine contraction and ends when the contraction relaxes. This is the normal bradycardia seen in labour due to compression of the fetal head aganist the maternal pelvis by the contracting uterus, thus, stimulating the vagus nerves.

The second type, "late deceleration", is felt to be due to placental insufficiency during a contraction. This bradycardia begins 20-30 seconds after the uterus begins contracting and lasts a similar length of time after the uterus relaxes.

The third type, "variable deceleration", is due to cord compression. The fetal heart rate is highly variable in its degree of slowing and in its time of onset relative to uterine contraction.[5]

(b) *Tachycardia* – The significance of fetal tachycardia, which is usually defined as a rate greater than 160 beats per minute, is unclear, but warrants a search for more dangerous signs. Hon feels that mild tachycardia may be an early sign of fetal distress.[5]

(c) *Irregularity of Heart Rate* – It is generally held that irregularity of the fetal heart rate by itself shares the same significance as fetal tachycardia. However, irregularity coupled with bradycardia indicates a worsening situation.[6]

(C) Special Studies

(1) *Detection of Meconium Staining*

Meconium (*Greek – poppy juice*) is a combination of mucoproteins, mucopolysaccharides, liquor amnii, bile, epithelial cell debris, and several other materials. Passage of meconium occurs under two conditions: fetal abdominal compression (as in some uncomplicated breech deliveries), and hypoxia which stimulates the colon and relaxes the anal sphincter.[6] When hypoxia is the cause, it produces some degree of fetal distress at that time, and meconium is passed. The fetus may either remain in distress or return to its previous normal intrauterine state. Therefore, many normal vertex presentations have been found to be associated with meconium staining, but with no fetal compromise.

Meconium may be detected by aminocentesis, amnioscopy, or when the membranes rupture.

(2) *Low fetal pH*

After the membranes have ruptured, the metabolic state of the fetus can be directly evaluated by analyzing small quantities of blood taken from the presenting part of the fetus,[7] by such techniques as those described by Saling.[8] The acid-base state of the fetus has proved to be a reliable indicator of the degree of intrauterine asphyxia. It has been observed that a fetal pH of more than 7.27 is usually associated with an Apgar score of 7-10, while a pH of less than 7.22 is associated with a score of 6 or less. Haworth et al state that if the pH is 7.2 or lower on two consecutive samples taken one hour apart, delivery should be carried out promptly.[9] Fetal pH determinations can also be a useful guide in deciding to delay delivery if the pH is normal, even though other signs or tests indicate much worse fetal distress.

(3) *Amniotic fluid analysis*

Abdominal amniocentesis has gained more support in recent years as a relatively safe, useful procedure. It is used mostly in suspected cases of Rh sensitization in order to measure the bilirubin level by spectrophotometric analysis. The pH, $pO_2$ and $pCO_2$ measurements can also be performed on the fluid since pH and $pO_2$ fall and $pCO_2$ rises with fetal compromise, although this is not always the case. It is, of course, useful also in detecting the presence of meconium.[10]

(4) *Hormone Changes*

(a) *Estriol*

During normal pregnancy, 90% of the estrogenic substances excreted in the maternal urine are in the form of estriol glucosiduronate. Estriol is produced by the foeto-placental unit, and, thus, serial determinations of estriol excretion are a most useful diagnostic tool.[11] It must be remembered that there is a wide range of normal values (12 - 40mg/hr.) and that a day to day variation of 30% in excretion at term may be normal.

Some authors point to absolute values as meaning fetal distress. For example, Willows uses 4 mg/24hr. as the critical value at term below which there is a poor fetal prognosis.[12] But a single estimation is worthless, and a better rule points to the pattern of serial determinations. In particular, if a fall of 50% or more of a previous estimation is noted, or two falling values are recorded in succession, fetal distress is likely.

(b) *Human Placental Lactogen (HPL)*

HPL is a hormone of placental origin which is measurable in maternal serum as early as 8 weeks gestation. There is a gradual increase in levels to the third

trimester where there may be more than a tenfold increase in the blood level. Urinary excretion parallels the serum levels of this hormone. Serial determinations can be used as with estriol to aid in diagnosing fetal distress. Again, absolute values are not as important as a trend to lower values.[13]

(5) *Enzyme Changes*

(a) *Serum Alkaline phosphatase*

Although the concentration of this enzyme in maternal serum increases during pregnancy, and there is evidence that part of the enzyme complex may be specifically derived from chorionic villi, measurement of this enzyme has not proved helpful.[11]

(b) *Diamine oxidase (DAO)*

This enzyme, supposedly derived from decidua. also rises during pregnancy, with the greatest increase in the first trimester. Resnik recently concluded that in the diagnosis of foetal distress DAO measurement is not useful.[14]

(c) *Oxytocinase*

Oxytocinase is produced by the placenta. Its levels in serum increase during pregnancy. It is rarely used to diagnose fetal distress.

## TREATMENT

The management of fetal distress is still empirical and can be stated rather simply: correct the environmental condition that is causing the fetal distress, or deliver the fetus into an adequate one.[4]

The ideal management of fetal distress is prevention. Here, of course, antepartum care is most important. A general medical history and physical examination in addition to the obstetrical history and examination, will alert one to possible problems. Regular return visits enable the doctor to follow the progress of the pregnancy and institute appropriate therapy as required.

(a) Acute Fetal Distress

Therapy can be considered in relation to the clinical picture. Fetal heart changes and meconium staining are the two most important signs of possible fetal distress.

(i) *Fetal Heart Changes*

1. *"Late Deceleration"* – As mentioned earlier, this type of bradycardia is due to placental insufficiency and is more sinister than variable deceleration. Although oxygen in high concentrations is commonly given to all mothers of cases of fetal distress, Hon feels that "late deceleration" type is the pattern most likely to improve with oxygen. If the mother is being stimulated with oxytocin, it should be discontinued.[5] Serial pH determinations can be taken, and, if consistently low or falling, they may indicate that delivery is necessary.

2. *"Variable Deceleration"* – Position change, whereby the mother is placed on her side or in the Trendelenburg position, may relieve cord tension or compression. If due to a prolapsed cord, acute fetal distress is treated by placing the mother in The Trendelenburg position and giving her oxygen. The fetal presenting part must be displaced from the cord by a sterile gloved hand. Delivery is carried out as soon as possible unless the fetus is dead.[5] If the cervix is fully dilated, low or mid-forceps delivery is indicated for vertex presentations, and total breech extraction is used if a breech presents. If incomplete dilation exists, abdominal delivery must be performed.[15]

With occult cord problems, no prolapse is seen and increasing distress is indicated by the progressively increasing duration of episodes of "variable deceleration."

(ii) *Meconium staining*

Since this may or may not be associated with fetal distress when discovered, other confirmatory signs should be sought. Frequent fetal heart auscultation or electronic fetal heart monitoring should be employed. Serial determinations of the pH of fetal blood (membranes ruptured) are useful in indicating the need for surgery, as described earlier.[15]

(b) Chronic Fetal Distress

This is usually associated with placental insufficiency, and there are a number of maternal and placental causes (see Etiology). Clinically identifiable distress is often supported by laboratory evidence, such as decreased estriol levels. Definite rules for therapy tend to break down in these situations, and only general guidelines can be given.

Control of the underlying disease, such as diabetes or toxaemia, may relieve placental insufficiency. One attempts to prolong pregnancy to 36-37 weeks gestation to avoid prematurity, but, procrastination in the face of advancing clinical and laboratory signs of placental insufficiency is poor treatment. Instead, delviery is required and commonly Caesarian section is undertaken to avoid difficult labour.[15]

## PROGNOSIS

The presence of any single sign of fetal distress means about a doubling of the stillbirth rate, while a combination of two such signs is associated with a fetal loss rate of 20-30%.[1] Cox's study shows that tachycardia, bradycardia or meconium passage each are associated with a 3-5% fetal mortality, but a combination increases the figure to 35%.[16]

No good studies are available concerning the effect of fetal distress on those babies who survive. However, there is a correlation between fetal distress and low Apgar scores at birth, as seen in Fisher's study.[17]

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BIBLIOGRAPHY

1. Eastman, N. J. and Hellman, L. M.: *Williams Obstetrics,* Appleton-Century-Crofts. New York, 1966 pp. 612-638 and pp. 924-937.
2. Naftolin, F.: *Vasa Previa - 3 Cases,* Obstetrics and Gynecology, vol. 26: 561-5, Oct. 1965.
3. Niswander, K. R. and Ray, M.: *Management of Second and Third Trimester Bleeding,* in Controversy in Obstetrics and Gynecology, Reid & Barton, Saunders, Toronto, 1969 pp. 70-75.
4. Davis, M.E.: *Management of Fetal Distress* pp. 258-65. Controversy (see 3).
5. Hon, E. H.: *Management of Fetal Distress* pp. 239-48.
6. Browne, F. J. and McClure Browne, J. C.: *Postgraduate Obstetrics and Gynecology,* 3rd Edition, Butterworths (London) 1964, pp. 714-720.
7. Duhring, J. L. and Greene, J. W.: *Evaluation of the Intrauterine Fetal Status,* Clin. Obst. Gynec. vol. 9: 935-43, Dec. 1966.
8. Saling, E.: *Foetal & Neonatal Hypoxia,* Arnold Pub. Ltd., London, 1968, pp. 74-114.
9. Haworth, S. G.: *Biochemical Indices of Fetal Condition,* Clin. Obstet. Gynec. vol. 11: 1182-1205, Dec. 1968.
10. Barnes, A. C.: *Intra-Uterine Development,* Lea & Febriger, Phil., 1968, pp. 447-497.
11. Klopper, A. and Diczfalusy: *Foetus and Placenta,* Blackwell, Oxford, 1969, p. 471-555.
12. Willows, R. L.: *Urinary Estriol Estimations in Normal and Abnormal Pregnancies,* CMAJ, vol. 94: 1098-1101, May, 1966.
13. Greene, J. W. and Tweeddale, D. N.: *Endocrine Indices of Fetal Environment,* Clin. Obstet. & Gynec., vol. 11: 1106-1120, Dec. 68.
14. Resnik, R. and Levine, R. J.: *Plasma Diamine oxidase activity in pregnancy: A Reappraisal,* American Journal Obstet. & Gynec., vol. 104: 1061-6, Aug. '69.
15. Nesbitt, R. E. L.: *Management of Fetal Distress,* in Reid & Barton's Controversy in Obstet. & Gynec., p. 249-257, 1969.
16. Cox, L. W.: *Fetal Distress,* Austral. & New Zeal. J. Obstet. & Gyn., vol. 1: 99, 1961.
17. Fisher, E. L.: *Prognosis in Fetal Distress,* Obstet. & Gyn., 24: 757-9, Nov. '64.

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# PAEDIATRICS

## *Salicylate Poisoning In Children*

*Michael F. Smith, 7T1*

### INTRODUCTION

Accidents are the leading cause of death and disability for Canadians between the ages of 1 and 39 years. Through our demand for greater comfort and a fuller enjoyment of our environment, we have ironically provided ourselves with commercial products and situations which claim more lives than any other medical or public health problem. In the home alone, over 500,000 domestic products have been incriminated as potential poisons, a staggering list which acquires 1,500 additions each month. It is not surprising to recognize that the incidence of accidental poisoning by ingestion of these toxic substances is highest among children 1 to 4 years old whose innocent curiosity compels them to sample any accessible item, and yet whose tolerance to such metabolic loads is small.

The salicylates are the most common substances involved in the accidental poisoning of children and account for 33% of poisoning deaths. They are used by almost every home in the form of aspirin for their analgesic and anti-pyretic properties and are considered by most to be a very innocuous household commodity. Nevertheless, from 1961 to 1969, the Hospital for Sick Children in Toronto treated 13,761 cases of accidental poisoning; of these 5,102 or 37.1% resulted from salicylate ingestion requiring 425 admissions and causing 9 fatalities.

The survey of accidental poisonings in Canada for 1965 to 1967 reported 23,944 cases of salicylate intoxication and showed children's flavoured aspirin to be responsible for 57.5% of cases, adult aspirin 18.9%, and other or non-specified salicylates 23.5%. The latter includes oil of wintergreen, a pleasant-smelling preparation used for muscle and joint pain, but which contains 98% methyl salicylate and is extremely toxic to young children.

Poisonings are acute medical emergencies demanding immediate treatment. Before salicylate intoxication can be intelligently managed, it is best to have an understanding of the pathophysiology of the response to salicylate ingestion.

### SALICYLATE PHARMACOLOGY

The salicylate compounds are rapidly absorbed from the mucosal surfaces of the gastro-intestinal tract, predominantly in the upper intestine, by passive diffusion of the undissociated molecule. The presence of salicylates in the blood and urine can be detected as early as 30 minutes after ingestion and peak levels in the serum are reached after 2 hours. On reaching the plasma, 50 to 80% of salicylates are bound to albumin, while the remainder readily diffuses into all body tissues and crosses the placental barrier. Methyl and acetyl esters are rapidly hydrolyzed to salicylic acid in the liver. Factors controlling plasma levels therefore include the initial dose, the protein content of the plasma, the time interval since ingestion, and the rate of elimination.

The half life of salicylates in humans is about 20 hours. Renal excretion is the principal route of elimination because very little of the ingested dose is degraded by metabolic pathways. The actual proportion of free, unaltered salicylate in the urine varies according to the urine pH. In alkaline urine the salicylate is trapped in the tubule in its dissociated form, unable to diffuse back into the renal parenchyma and the free salicylates may reach 85%. In acid urine the undissociated form freely diffuses back and may thus only account for 10% of the excreted salicylate. When oil of wintergreen has been ingested, the free methyl salicylate imparts its characteristic odour to the urine. The remaining salicylate lot is excreted conjugated with glycine as salicyluric acid or as phenolic and acyl glucuronides.

Salicylic acid itself is intensely irritating to the skin and mucosa and its use is restricted primarily to the removal of warts. Salicylates are usually administered as the acetyl or sodium esters and are given orally. Their pharmacological actions account for the somewhat confusing clinical picture of salicylism.

#### 1. Central Nervous System

The CNS is the site of many important effects. When the body temperature is elevated, salicylates have an antipyretic effect by resetting the hypothalamic thermostat to a more normal level. Heat loss is augmented by hypothalamic originated peripheral vasodilation and sweating.

Analgesia against low intensity pain from integumental structures (headache and arthralgia) is mediated by depression of the CNS through an unknown mechanism. Salicylates may greatly potentiate other analgesics when used in combination with them. Higher doses may actually stimulate or depress the CNS itself and be manifest in striking changes of behaviour. Nausea and vomiting, mediated through the vagus, are caused by central stimulation beside the presence of peripheral gastric irritation.

Another CNS effect very pertinent to salicylate intoxication is the direct stimulation of respiration by $CO_2$ sensitization of the respiratory centre in the medulla. Ventilation may increase in depth and rate by a factor

of 10 times the basal level. A relative respiratory alkalosis develops. Sustained high doses may eventually lead to central respiratory depression and a subsequent respiratory acidosis. Salicylates also indirectly stimulate respiration by increasing $O_2$ consumption and $CO_2$ production through metabolic pathways.

2. Metabolism

Salicylates uncouple oxidative phosphorylation in a manner reminiscent of 2,4-dinitrophenol which reduces the efficiency of ATP dependent reactions and inaugurates compensatory oxidative mechanisms. This boosts the metabolic rate and increases oxygen consumption and carbon dioxide production and heat energy. Enhanced respiration, cardiac output, and heat dissipation are required to accommodate this change. Carbohydrate metabolism is altered and manifest by either hypoglycemia or hyperglycemia. Increased metabolic rate, tissue utilization, and salicylate inhibited gluconeogenesis may account for hypoglycemia. Hyperglycemia may be partly explained by the release of epinephrine through hypothalamic sympathetic discharge.

Additional metabolic effects include a shift towards a negative nitrogen balance and increased fat metabolism in muscle.

3. Renal Effects

A well documented effect of salicylates on renal function concerns uric acid and excretion. Daily doses of 1 to 2 g. decrease uric acid loss; daily doses of greater than 5 g. increase uric acid excretion.

It is postulated that salicylates have a specific action of decreasing the reabsorption of bicarbonate ions on the renal tubular cells.

4. Gastrointestinal Tract

Gastrointestinal manifestations of salicylate include vomiting (central and peripheral origins) and varying degrees of mucosal irritation which may lead to actual hemorrhage and anemia. Salicylates may cause pylorospasm and delayed gastric emptying; a salicylate bolus may be formed which is inaccessible to gastric lavage.

5. Cardiovascular System

In addition to the vasodilation of the hypothalamus, there is a peripheral relaxation of vascular tone directly resulting from the effects of salicylates on the smooth muscles of the vessel walls. The cardiovascular system is further depressed by the toxic action of salicylates on the vasomotor centre itself.

Reduced blood coagulability can be demonstrated by a prolonged prothrombin time. This problem is usually seen in chronic, high dose therapy and explained by a fall in plasma prothrombin level. Vitamin K reverses the defect.

6. Endocrine System

Some minor endocrine changes have been observed. The adrenal medulla apparently secretes epinephrine through salicylate induced hypothalamic discharge. In large doses, increased secretions of the adrenal cortex are thought to follow a rise in ACTH secretion. Chronic therapy is also associated with an increased protein bound iodine level.

The anti-inflammatory and antirheumatic action of the salicylates is still a mystery. However, it is known that high doses will inhibit the action of many enzymes similar to hyaluronidase.

Caution should be exercised in the administration of acetylsalicylic acid to asthmatics or to patienst with a history of allergies, for it may precipitate an attack, particularly in children. This idiosyncrasy of response may present as a minor skin eruption or as a generalized anaphylactic reaction with asthma, angioedema, and laryngeal swelling with life-threatening asphyxia. Epinephrine usually controls the edema, but the asthma may be refractory to treatment.

## PATHOPHYSIOLOGY OF SALICYLATE POISONING

Salicylate poisoning may result in children from either acute ingestion of a bolus dose with blood levels greater than 160 mg.% or from chronic therapeutic overdose in which blood levels need not exceed 15 mg.%. The usual lethal dose for children varies from between 8 and 60 g. of aspirin. Much more potent methyl salicylate may be fatal in a dose of 4 ml. or 2.7 g.

The pathological mechanisms which underly salicylate poisoning are closely bound to the pharmacology of the drug and to the physiological response of the patient to compensate for the induced changes in body chemistry. Children are more vulnerable to these changes because of their smaller reserve in metabolic adaptability and may develop much more serious problems than adults, despite comparable doses.

Salicylate intoxication produces changes in the acid base balance of body fluids coupled with critical alterations in plasma electrolytes which are aggravated by dehydration and hyperpyrexia. Usually, it is the hyperpyrexia and ultimate respiratory failure which prove fatal. The terminal clinical picture is totally unpredictable because of the many variable, opposing processes involved.

The initial response to salicylate ingestion in all patients is a centrally stimulated hyperventilation which reduces the $pCO_2$ and increases the blood pH to produce a respiratory alkalosis. Coincident with the pH change is a compensatory renal excretion of bicarbonate with potassium and sodium. The reduction in plasma bicarbonate returns the pH to normal and a totally compensated respiratory alkalosis is achieved. However, in

order to compensate for this alkalosis, the reduced bicarbonate and potassium levels leave the extracellular and intracellular buffering capacities considerably diminished.

In children, subsequent changes occur only after toxic doses have been ingested. In these situations, the compensated respiratory alkalosis is only transient, for very rapidly a combined metabolic and respiratory acidosis may develop. As toxic levels are reached, the respiratory centre is eventually depressed and the increased production of $CO_2$, from the high metabolic rate, overcomes its alveolar excretion. The $pCO_2$ rises to about normal from its reduced level and an acidosis emerges, because the buffer base lost through renal excretion has not been replaced.

Gradually, the metabolic component to this acidosis increases as the salicylates begin to interfere with carbohydrate metabolism and lipolysis substitutes for the normal pathways. Organic and ketoacids, mostly pyruvic, lactic, and acetoacetic acid begin to accumulate. Because of the salicylate induced vasodepression, renal blood flow and glomerular filtration rate fall and the kidney is less able to excrete acids of metabolic origin, namely phosphoric and sulfuric acids. Salicylic acid itself dissociates at blood pH and further displaces 2 to 3 mEq of bicarbonate. The buffering systems, previously depleted by the transient respiratory alkalosis, are now completely unable to compensate for this new acidosis. Blood chemistry results at this point usually reveal a low pH, normal or slightly elevated $pCO_2$ and an extremely reduced bicarbonate level, often below 10 mEq/L.

The development of an early alkalosis by hyperventilation is opposed by the increased metabolic production of $CO_2$ and organic acids. The resulting effect cannot be anticipated, but depends on which of these two processes predominates. Should salicylate levels be high enough to produce toxic respiratory depression, it is obvious that a profound acidosis will quickly develop.

The electrolytes will vary as widely as the acid base disturbances, but generally speaking, the bicarbonate values are very low. Although much sodium is lost through the kidney, the insensible loss of water through the skin and respiratory tract is greater than electrolyte loss. Therefore, dehydration is usually associated with hpernatremia. Total body potassiu mis reduced; this is usually reflected in the serum unless acute tubular necrosis or renal failure develop, in which case serum potassium values will be high. After the renal dumping of bicarbonate in early acidosis, chlorides are usually elevated; this may be reversed if vomiting has been significant.

The change in blood glucose levels cannot be used to assess the child's progress or clinical status in any reliable way. Younger children seem to suffer more violent alterations in blood glucose, but its only significance is found in hyperglycemia where the diferential diagnosi of diabetic ketoacidosis must be excluded.

A secondary dehydration develops subsequent to the solute load diuresis of early respiratory alkalosis, anorexia, occasional vomiting, salicylate induced sweating, and insensible water loss through the skin and lungs. In the face of a stimulated metabolic rate, this dehydration greatly compromises the heat loss mechanisms of sweating and peripheral vasodilation, which may even be replaced by vasoconstriction should the blood volume fall to shock levels. The end result of this predicament is a rapidly, uncontrollably rising body temperature which may be lethal to the child in a very short time.

## CLINICAL FEATURES

The typical child suffering from salicylate poisoning is the adventurous, inquisitive toddler, 1 to 3 years old, who has eaten a variable quantity of aspirin tablets and is brought to hospital by an anxious parent. The history commonly reveals that the child vomited several times about an hour after the estimated time of ingestion and then, 2 or 3 hours later, began to breathe deeply and may have shown some evidence of irritability and restlessness. The early stages of salicylate intoxication usually follow this pattern, but the presenting picture of the patient will vary greatly according to several important factors.

Age is a major determinant, for the ability of the infant to tolerate the metabolic load imposed by the salicylates in much lower than older children. Children less than 4 years old tend to present in acidosis, whereas older children and adolescents, with a greater metabolic reserve, more commonly present in alkalosis.

The post ingestion interval is a very important parameter to determine from the history because the correlation between the clinical severity and the *stat* serum bicarbonate and salicylate levels is very unreliable unless the time elapsed since ingestion is known. The true clinical severity and prognosis do correlate well to the time zero salicylate level which can be extrapolated from the Done Nomogram in cases of single dose ingestions.

The presence of chronic disease and a history of chronic salicylate therapy places the symtomatic child in a more serious category, for the effects tend to be cumulative. The patient may be receiving aspirin, for example, as treatment for Still's disease and either be given an accidental overdose or develop an intercurrent infection which then precipitates the symptoms of intoxication. Acute pneumonia is a very pressing complication because it deprives the child of normal respiratory reserve.

Regardless of the difference in clinical presentation there are some helpful generalizations which distinguish the mildly affected from the severely poisoned child.

Mild salicylism typically presents as hyperventilation with a biochemical picture of respiratory alkalosis in the

child older than two years. Other symptoms will likely include sweating, thirst, dizziness, and some nausea and vomiting.

Moderately severe intoxication demonstrates a greater predominance of the metabolic effects of salicylate. They are quite often febrile and somewhat dehydrated. CNS disturbances are manifest by vertigo, restlessness, tremor, and incoherent speech. The more severely affected children in this group may demonstrate the "salicylate jag", a behavioural change ranging from garrulity to maniacal delirium and hallucinations. Electrolyte and acid base changes confirm metabolic acidosis.

The child who presents with severe salicylate poisoning is a critically ill patient. The prominent feature is often toxic encephalopathy which may vary from convulsions, very difficult to differentiate from chorea, to coma attributed to extreme hyperpyrexia and acidosis. The moderate or severe dehydration may place them in shock, and rarely cause acute tubular necrosis. The patient is often breathing with Kussmaul respiration, desperately fighting to reduce the acidosis while faced with the threat of respiratory depression. Infrequently, myocardial decompensation may occur from the acidosis, potassium deficiency, hyperpyrexia, and inadequate carbohydrate metabolism and congestive heart failure ensue.

## DIAGNOSIS

The diagnosis of salicylate poisoning is rarely a problem because the history of salicylate ingestion is most often well known by the parent. Should there be some difficulty in identifying the toxic substance, salicylism can be easily confirmed by the analysis of urine, vomitus, or blood. A simple screening test using Phenistix can be specifically employed to detect serum or urine salicylate without false positive results from either ketones or phenothiazines.

The discovery of urine salicylate is of great importance in ruling out the differential diagnosis of diabetic ketoacidosis.

## MANAGEMENT OF SALICYLATE POISONING

The rationale of treatment for salicylism follows the principles of treatment for any poisoning. The physician must rid the body of the noxious substance, correct the deficits incurred by the response to this substance, and provide supportive therapy as required. There is no dogmatic prescription for salicylate poisoning. The immense variability of presentation and response necessitates that the treatment be individually tailored to each patient and his recovery carefully scrutinized.

Fluid replacement, which is the *sine qua non* of treatment, must be calculated with regard to the patient's age and weight, the degree of dehydration and clinical severity, and laboratory data. Imperative laboratory investigations are serum salicylate and bicarbonate levels, blood pH, and electrolytes. Replacement therapy is a very delicate procedure in children and parameters of response should be measured every half hour in critical cases.

Mild intoxication may only require oral hydration with minimal electrolyte replacement and observation. Severe salicylism will demand as aggressive a treatment as the centre can provide.

As soon as possible, direct removal of ingested salicylate should be attempted by inducing vomiting (only if the patient is awake and alert). This is best accomplished by syrup of ipecac 10 to 15 ml followed by 100 to 200 ml of water. The vomitus should be analyzed; tablet fragments are a good prognostic sign. Gastric lavage followed by aspiration is not as efficient or pleasant but may be necessary in an uncooperative youngster.

Early emergency complications may arise suddenly which must be dealt with swiftly. Hyperpyrexia must be reduced by sponging with tepid water to avoid aggravating vasoconstriction. Convulsions and seizures must be treated quickly with a non depressing drug like paraldehyde because of the risk of respiratory depression. The very short acting barbiturates like thiopental sodium may be used if necessary. Respiratory assistance should be available for the patient who is unable to maintain a sufficiently low $pCO_2$ to avoid a fatal acidosis.

Intelligent management requires laboratory investigations to supplement the physician's clinical appraisal. These will include:

1. Hemoglobin, white blood cell count, hematocrit.
2. Blood urea nitrogen and blood glucose.
3. Serum salicylate by the Trinder method.
4. Serum electrolytes (Na, K, Cl).
5. Serum bicarbonate.
6. Blood pH.
7. Urinalysis.

Administered fluids must supply daily maintenance requirements, correct for shock and electrolyte deficits, and replace additional water lost through the lungs and skin. Adequate fluid therapy will restore renal blood flow and glomerular filtration rate, prerequisites to the excretion of salicylates. Seriously ill children should be catheterized to permit accurate assessment of their fluid balance.

Serum electrolytes must be watched closely. Potassium is usually deficient and should be administered after a diuresis has been established. If the serum sodium rises above 155 mEq/L, the sodium in the IV fluids should be reduced by 25 to 50%.

The use of sodium bicarbonate to increase salicylate renal excretion and to reduce severe acidosis is still being debated. The disadvantage encountered is the precipitation of a metabolic alkalosis as the patient recovers. This has led to acute pulmonary edema and tetany involving the glottic musculature. However, these dan-

gers can be avoided by the careful observation of the patient's blood pH and bicarbonate level, and occasionally by the prophylactic use of calcium gluconate.

The following regime of electrolyte and fluid replacement is very simple, but it provides a sound initial plan which can be altered as the patient responds:

1. The symptomatic patient whose salicylate level is in the order of 50 to 80 mg%.
   IV 5% D/W in 0.5N saline to run at 3 L/M²/24 hours
   KC1 3 mEq/kg/24 hours after diuresis established
2. The symptomatic patient with acidosis and dehydration.
   IV as above but to include $NaHCO_3$ 3 mEq/kg over one hour.
   In severe dehydration, IV to run at 3.6 L/m²/24 hours.

Recently, the use of acetazolamide has become more popular. This carbonic inhibitor alkalinizes the urine but contributes to the metabolic acidosis. It can be used safely when the excretion of salicylate is important but acidosis and dehydration have not yet developed. Bicarbonate may be used to correct secondary acidosis.

The child who remains in shock and is oliguric after hydration or who develops acute renal failure and coma should be treated by dialysis. Hemodialysis or exchange transfusion are often not available; peritoneal dialysis is usually adequate if carried out every 6 to 8 hours two or three times. One litre of albumisol to which has been added 5 mEq KCl and 500 units of heparin should be added after three hours.

Further details regarding treatment are beyond the scope of this paper but may be found in the reference listed at the end.

## CONCLUSION

Acute and chronic salicylate poisoning present in children as a pressing medical emergency which in most cases can be adequately treated if medical attention is sought in time. Treatment alone will not solve the problem. Only through the education of parents and the improvement of child-proof packaging can we hope to reduce the high incidence of accidental salicylate poisoning.

## REFERENCES

1. Varga: Handbook of Pediatric Medical Emergencies. 4th Edition, 1968.
2. Goodman and Gilman: The Pharmacologic Basis of Therapeutics. 3rd Edition, 1967.
3. J. C. Hughes: Synopsis of Pediatrics. 2nd Edition, 1963.
4. Whitten et al: Managing Salicylate Poisoning in Children. American Journal of Diseases in Children. Vol. 101, February, 1961.
5. R. Fay: Salicylate Poisoning in Children. New York State Journal of Medicine. Vol. 69, December, 1969.
6. W. E. Segar: The Critically Ill Child. Paediatrics. Vol. 44, September, 1969.

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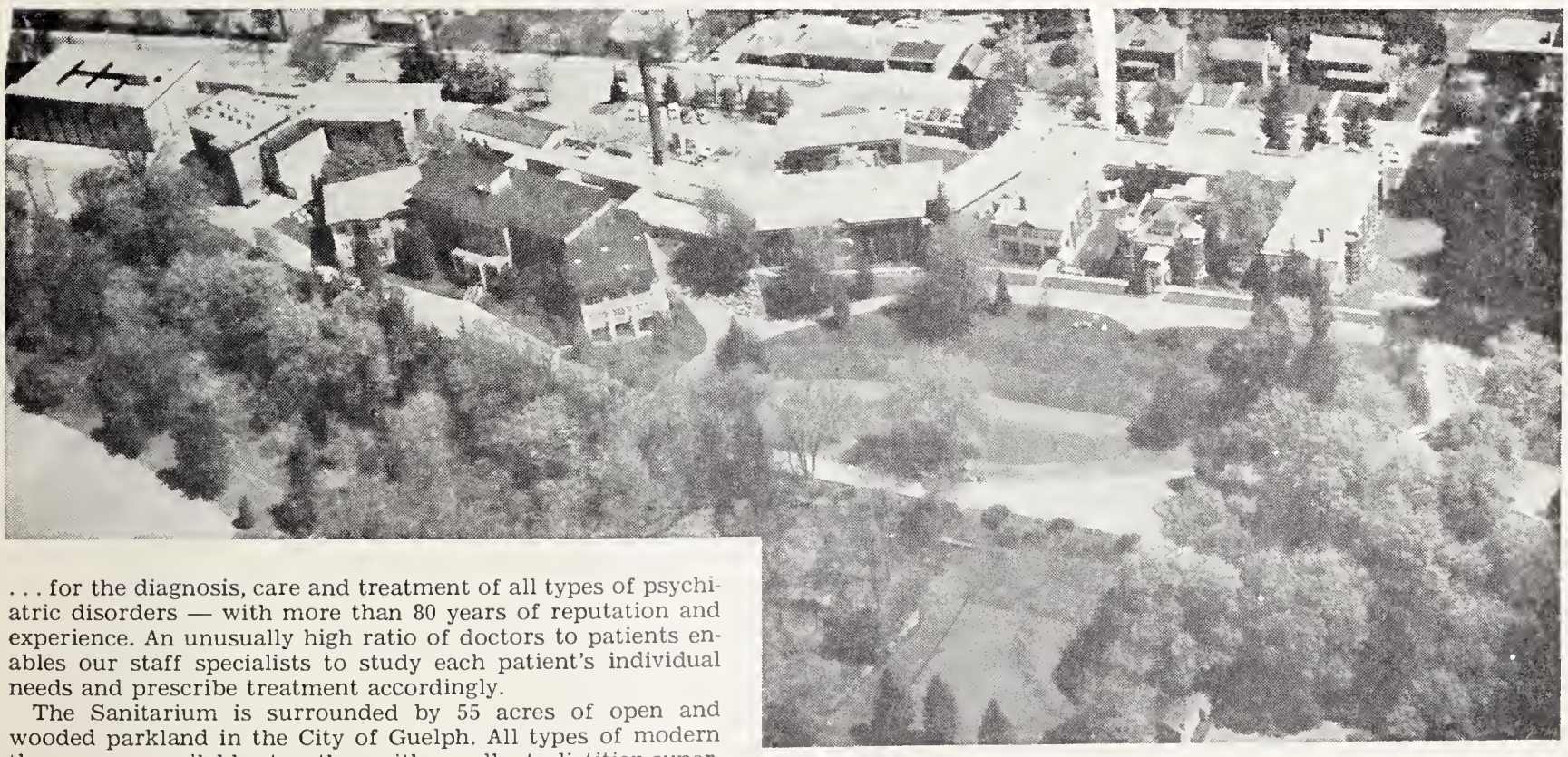

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# *Diagnosis And Treatment Of Pulmonary Embolism*

## INTRODUCTION

Thromboembolic pulmonary disease is a common occurence, confined neither to the elderly nor to those who appear ill but affecting all age groups, children included. Although pulmonary emboli can take the form of fat droplets, air, tumor, or amniotic fluid, this article will deal only with thrombotic emboli arising in systemic veins or the right side of the heart, and carried to the lung.

## CLINICAL PICTURE

The clinical picture is extremely variable, encompassing a condition in which symptoms and physical signs are non-existent, as well as a fulminant state where death may occur within minutes. The obstruction may be complete or incomplete, may be central, as when the blood flow to a large part of the lung is compromised, or peripheral, in which case only a small area of the lung is affected. These variables strongly influence the clinical state of the patient and his prognosis.

"Air hunger" leading to tachypnoea is one of the most reliable and consistent signs. Cyanosis, on the other hand, does not occur in mild to even moderately severe cases, as ventilation of the affected lung is not grossly altered. However, when a significant area of the lung is well ventilated but poorly perfused, e.g. massive central pulmonary embolism, cyanosis is likely to be present. Bronchoconstriction frequently accompanies the acute episode, adding to the air hunger and giving rise to ronchi on auscultation. There may also be signs and symptoms suggestive of pulmonary infarction when the vascular flow to a segment of lung is completely obstructed by either the original embolus, or appositional growth. The pain of pleuritis may be present. If the diaphragmatic pleural surface becomes involved, pain may be misinterpreted as being abdominal in origin. Frequently, infarction is accompanied by hemoptysis; decreased movement of the affected hemithorax; a friction rub, increased intensity of breath sounds, dullness to percussion, fever and, with the passage of time, a pleural effusion. Pain of pleural irritation most likely will not be confused with pain of cardiac origin. However, dilation of the larger pulmonary arteries due to massive embolism may give rise to pain very similar to that of angina pectoris. Obstruction of right ventricular outflow will result in fixed splitting of the second heart sound. Right heart failure may occur. This is more probable in the presence of concurrent myocardial disease and is accompanied by a right ventricular gallop rhythm. This, as well as increased central venous pressure and hypotension are poor prognostic signs although the latter two may not be present initially. In the case of central venous pressure, sequestration of blood in the lower extremities by femoral or pelvic thrombi may inhibit its early elevation. Similarly, reflex peripheral vasoconstriction will obscure an early development of hypotension. The eventual fall in blood pressure is associated with a rapid pulse rate with decreasing amplitude. The combination of respiratory distress, sudden collapse, rapid weak pulse, hypotension and a right ventricular gallop rhythm, suggests an acute emergency situation.

The physician may be tempted to find signs of deep vein thrombosis of the legs before making a diagnosis. Emboli, however, may also arise from deep pelvic veins, the right side of the heart, and elsewhere. Signs of leg or peripheral vein thrombosis are often absent or may not reveal themselves until several days later.[1]

## DIAGNOSIS

Certain groups of patients are more prone to the development of thromboembolic phenomena, and thus a greater index of suspicion is assigned to them. One important precipitating factor is venous stasis associated with inactivity seen in prolonged illness, the post-surgical patient (especially when the surgery has involved abdomen or lower extremities), post partum, extensive trauma, prolonged anaesthesia and congestive heart failure. A second factor, increased propensity to form clots, is seen in the post-splenectomy patient, polycythemia, and in certain susceptible individuals on oral oestrogens.

After physical examination, the three most important initial investigations are: serum enzyme levels, E.C.G., and plain chest films. These are necessary to rule out other acute situations and to substantiate the diagnosis of pulmonary embolism. With the wide range of signs and symptoms that can occur in this condition, a differential diagnosis should always be kept in mind.

This includes:

- acute myocardial infarction
- right heart failure
- acute cardiac tamponade
- pneumonitis
- acute internal hemorrhage (such as from a ruptured ectopic pregnancy)[1]

Serum enzyme levels to be investigated consist of LDH, SGOT, and CPK. LDH is almost specific for pulmonary embolism, beginning to rise promptly and reaching a peak 24 to 48 hours after the acute episode. Normal LDH levels in the first 48 hours tend to rule out pulmonary embolism. SGOT and CPK levels are meas-

ured primarily to rule out myocardial infarction in which the former rises to maximum levels in 24 to 48 hours, the latter in 12 to 48 hours. Both remain within normal limits after a pulmonary embolism.

The electrocardiogram, as well, is necessary in excluding primary myocardial disease and could even possibly point towards the lungs as the source of the problem. A normal ECG does not rule out the diagnosis of pulmonary embolism, since many of the changes tend to be transistory owing to the ability of the heart and the pulmonary vasculature to compensate rapidly in most cases. If the tracing shows evidence of right axis shift, right bundle branch block, or right ventricular strain, there is a high probability of major pulmonary embolism if the patient's ECG was known to be normal prior to the acute episode. With severe obstruction of the pulmonary arterial flow, the ECG may show changes resembling a posterior or inferior infarction. This may be due to decreased flow in the right coronary artery secondary to dilation of the right ventricle or to inadequate flow in both coronary vessels.[1] It should be noted that coronary arterial insufficiency leading to cardiac arrest is a major cause of death in cases of massive pulmonary embolism.

Plain chest films should also be done. However, they may appear to be entirely normal in a patient with relatively severe embolism. Like the ECG, they help to rule out pre-existing cardiac disease and possibly substantiate the diagnosis. The presence of a wedge-shaped defect in the plain film is rare. There may or may not be peripheral radiolucency due to the absence of vascular shadows, depending on the degree of arterial obstruction. The more complete the obstruction and the larger the vessel affected, the more likely dilatation of the hilar vessels will be seen. An entire pulmonary arterial branch may show fusiform dilatation. Should infarction occur, the early chest film may show patchy densities in the affected area, so ill defined that there may be some difficulty in distinguishing this from bronchopneumonia.[2] Diaphragmatic elevation should be noted in cases of infarction as well as some pleural effusion heralded initially by the presence of fluid in the costophrenic angle.

Further radiological studies are necessary in those cases where plain chest films cannot substantiate the diagnosis. The choice lies between lung scans and pulmonary arterial angiography. Lung scanning involves the intravenous injection of macro-aggregates of serum albumin labelled with $I^{131}$, followed by scanning of the chest by a scintillation camera or gamma camera (the latter being a more rapid procedure). It is a relatively innocuous procedure. In the pregnant woman, technicium labelled albumin should be used instead, due to the dangers of radioactive $I^{131}$ uptake by the fetus.

Angiography requires the injection of contrast material directly into the pulmonary artery so that filling of the cardiac chambers by radio-opaque dye will not obstruct the view of the hilar vessels. This necessitates the passing of a catheter through the right side of the heart, a procedure associated with a fair amount of morbidity. The catheter must be introduced via an arm vein in order to decrease the likelihood of freeing a thrombus from the walls of pelvic or leg veins, should the saphenous route be used.

Thus, a decision has to be made on which method to use and when. In most cases of pulmonary embolism, there is a high correlation between the findings of lung scans and pulmonary angiograms (see Fig. 1 and Fig. 2). Because of the decreased risk involved, lung scans should be the investigation of choice. False positives include lobar pneumonia, emphysematous bullae, pleural effusions and other space occupying lesions. In the presence of suspicious physical signs, focal segmental or lobar areas of decreased activity in the scan strongly suggest the presence of pulmonary embolism. Diffuse areas of radioactivity have a poor correlation. A "normal" lung scan should rule out any clinically significant embolism.

In the emergency situation where surgery is being contemplated, pulmonary angiography becomes the method of choice in spite of its greater morbidity. In these cases, the size and location of the embolus must be known prior to operation. For this purpose, angiography is the most definitive procedure. Many hospitals are not equipped to do lung scans on an emergency basis without excessive transport of the critically ill patient and the wasting of valuable time. Angiography tends to be more commonly used in these cases. However, if hypotension does not persist and the patient becomes stabilized with therapy, angiography may be undertaken several days after the acute episode in order to determine the extent of vascular involvement. It should be noted that chronic recurrent embolic disease may not produce an abnormal angiogram, and serial lung scans, if available, may be more useful.

Blood gases may serve to substantiate the diagnosis but are not essential in the emergency situation. Characteristically various degrees of hypoxemia result, depending on the degree of arterio-venous shunting. Air hunger leading to tachypnoea gives rise to hypocapnia. A decrease in $PO_2$ and $PCO_2$ is not pathognomonic of this condition. This blood picture is also seen, for example, in acute pulmonary oedemia.

## TREATMENT

Both medical and surgical methods of treatment are available and a choice *must* be made. A small number of patients – those with massive embolism – die rapidly within minutes or hours of the acute episode. It is unlikely that any of these patients could be saved by medical means. In a study of 100 cases of massive pulmonary embolism, 41 died within 10 minutes, 66 died within 2 hours, and 16 more over the next 22 hours.

It should also be remarked that a certain proportion of patients will survive with no treatment whatsoever. Overall, however, the untreated patient does have a higher mortality rate.

As soon as the condition is suspected, heparin therapy should be initiated. Heparin has an initial advantage over oral anticoagulants in that its action is more rapid in onset, and it tends to alleviate bronchospasm, possibly by the prevention of the release of serotonin by patients.[4] 10,000 to 15,000 units should be given initially intravenously with 10,000 units given additionally every 2 to 4 hours. Clotting times should be tested several times during the first 2 days in order to gauge individual response to the drug. The clotting time should be at least 2 to 3 times normal. Once the response to heparin is noted, dosages can be altered accordingly. The clotting time is then measured once daily. Alternatively, heparin may be given by continuous intravenous infusion, 40,000 units or more per day, with the same precautions taken regarding clotting time. Hemorrhagic complications must be watched for, especially in the elderly. Drugs which interfere with the ability of blood to clot, e.g. salicylates, clofibrate, quinidine, phenylbutazone, should be discontinued. Protamine sulphate, 1 mg./100 U. heparin (referring to the last injection) to a maximum of 100 mg. can be given for heparin overdose. Oral anticoagulants may be initiated at the same time as the heparin, but it is more usual to wait six to ten days. Prothrombin time should be 2 to 2.5 times normal and measured daily. Once this level has been reached, heparin may be stopped over the next 24 hours. The oral therapy should be continued for a minimum of 3 to 6 months.

Oxygen by mask or nasal catheter is indicated in many but not all cases. If the patient has only pleuritic symptoms attributable to a small peripheral infarction oxygen is not necessary. In the presence of hypotension, cyanosis, and air hunger, oxygen is indicated and should be given at the rate of 4 to 6 L./min. A patient with severe pain, right heart failure, respiratory distress or cardiac ischemia secondary to decreased blood flow through the lungs, may require morphine for relief of pain, anxiety, and agitation. Otherwise a milder analgesic will suffice.

A controversial method of treatment currently under investigation consists of the use of lysing agents in the treatment of thromboembolism. Heparin and the oral anticoagulants are primarily prophylactic agents for the prevention of appositional growth of emboli or the formation of new thrombi. Heparin has some spontaneous fibrinolytic activity in the bloodstream, but it is only capable of dealing with small fibrin deposits and smaller emboli and is not adequate for the lysis of emboli occupying longer stretches of an artery or vein.[5] Some lytic preparations currently being evaluated are streptokinase, urokinase, and ARVIN, an extract of the venom of the Malayan pit viper. Streptokinase, an enzyme produced by a strain of streptococci, is subject to the same antibodies produced in the body in response to numerous past or recent streptococcal infections. Its use is thus contraindicated when antibody titres are greater than 200 units/ml. of plasma, because of possible anaphylactic reactions. Urokinase is an enzyme extracted from human urine. It is a more powerful lysing agent than streptokinase, being a potent activator of the conversion of plasminogen (profibrinolysin) to plasmin (fibrinolysin). However, at the present time, the difficulties involved in purifying urokinase economically have not yet been overcome. ARVIN was found to have fewer side effects than the preceding drugs, but much less lytic activity.[6]

Aside from the problem of the side effects mentioned above there are other reasons why these drugs are not yet used routinely in the treatment of pulmonary embolism. The most important reason is that they do not always work. Secondly, they require time before they are effective. Thirdly, they cannot be used in patients with a low functional reserve. One study by Kakkar et al, has shown that at the present time, pulmonary angiography is the single most important procedure to utilize in order to determine which method of treatment should be used.[7] Poor results were obtained when the lytic agents were used in cases of complete obstruction, or after a period of 72 hours.[6] Eventually, the lytic agents may be modified or purified to the point where they could be as clinically acceptable as the anticoagulants currently are. It took 23 years between the discovery of heparin and its widespread clinical use.

Finally, embolectomy is utilized in the treatment of pulmonary embolism, although usually only of the massive type. Indications include persistent shock, increased central venous pressure, evidence of renal failure, continued hypotension (systolic pressure less than 100)[7]. Other factors are contraindications to the use of anticoagulants (which are also applicable to thrombolysins). These include bleedinig diatheses, suspected or proven gastrointestinal bleeding, hypertension, severe renal or hepatic disease, and recent surgery where bleeding constitutes a risk. Menstruation and a patient's age over 80 years can be considered relative contraindications, the latter due to increased permeability of vessels. The number of patients that require embolectomy is small, but as noted by Gorham, they tend to succumb rapidly without treatment. This surgical procedure requires a cardiopulmonary bypass, and a surgical team ready to operate at a moment's notice. Unfortunately this is not always possible so that in many hospitals, embolectomy is a relatively uncommon procedure. The operation is associated with a fair degree of morbidity and mortality. General anaesthesia is required, tending to work against peripheral vasoconstriction, enhancing any hypotension, and leading possibly to bradycardia and cardiac arrest. Vasoconstrictors may be necessary to counteract this. If the operation is a success, post-operative therapy in-

FIG. 1: A large pulmonary embolus obstructs the pulmonary artery to the right mididle and lower lobes (seen between the 2 black markers).

cludes the utilization of anticoagulants for 3 to 6 months or longer should evidence of deep vein or pelvic vein thrombosis be still present.[8]

## SUMMARY

History, physical examination, and a high index of suspicion play an important role in the diagnosis of acute pulmonary embolism. Initially the most important investigations needed to rule out other conditions in the differential diagnosis are ECG, plain chest films, and serum enzyme levels. Lung scans may be used to confirm the diagnosis, although pulmonary angiograms are the most definitive of all the tests and may be necessary in some situations. Treatment consists of intravenous heparin immediately on suspicion, oxygen, and other supportive therapy. Surgical intervention is indicated as a life saving procedure, in massive pulmonary embolism. Rapid thrombolysis, while not yet perfected, provides an interesting and probably fruitful goal for future research.

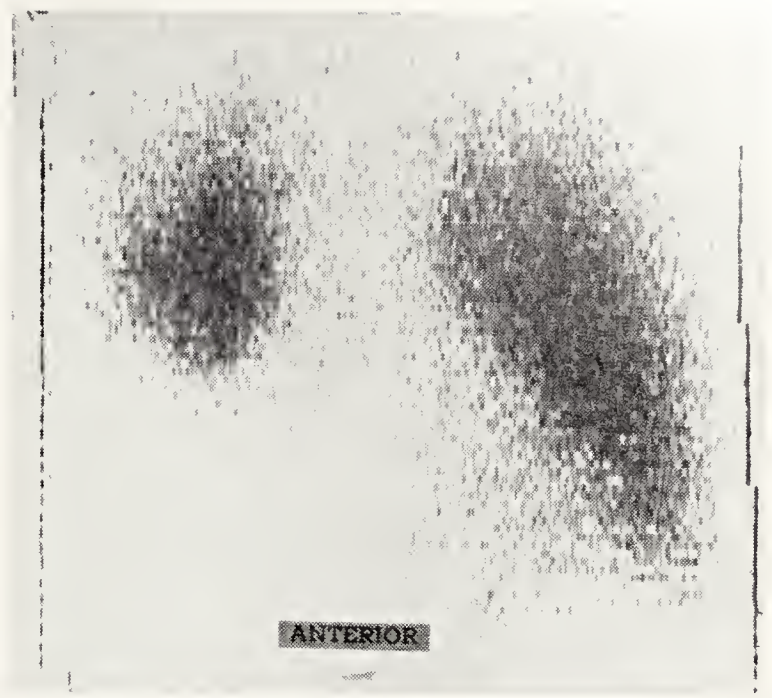


FIG. 2: The same patient as in Fig. 1, the lung scan shows focal loss of perfusion involving the right lower and middle lobes.

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## REFERENCES

1. Oakley, C. M.: *Diagnosis of Pulmonary Embolism*, British Medical Journal, 2: 773-777, June, 1970.
2. Meschan, I.; Farrer-Meschan, R.: *Roentgen Signs in Clinical Practice*, Vol. I and II, W. B. Saunders Co., 1966.
3. Gorhan, L. W.: *A Study of Pulmonary Embolism*, Archives of Internal Medicine, 108: 8-22, 1961.
4. Miller, G. A. H.: *Massive Pulmonary Embolism — Medical Management*, British Medical Journal, 2: 777-778, June, 1970.
5. Poller, L. (Ed.): *Recent Advances in Blood Coagulation*, J. and A. Churchill Ltd., 1969.
6. Kakkar, V. V.; Flanc, C.; Howe, C. T.; O'Shea, M.; Flute, P. T.: *Treatment of Deep Vein Thrombosis, Trial of Heparin, Streptokinase*, and Arvin, British Medical Journal, 1: 806-810, 1969.
7. Kakkar, V. V.; Raftery, E. B.: *Selection of Patients with Pulmonary Embolism for Thrombolytic Therapy*, Lancet, 237-241, Aug., 1970.
8. Paneth, M.: *Surgical Management of Massive Pulmonary Embolism*, British Medical Journal, 2: 778-779, June, 1970.

(Both case pictures courtesy of D. Gilday M.D., Dept. of Nuclear Medicine, University of Toronto)

*May Ho,* 7T1

# *Hyperglycaemic, Hyperosmolar Non-ketotic Coma*

In spite of recent advances in medical knowledge, the diagnosis and treatment of a comatose patient continues to baffle physicians and students alike. This is especially true of hyperglymaemic, hyperosmolar, non-ketotic coma (HHNKC) which was not recognized as a medical emergency until as recently as 1957. To date, a total of 137 cases have been reported, with only slightly greater than 50% survival. The high mortality rate has been attributed to 2 factors, failure to recognize the syndrome, and inappropriate therapy. While the deaths could have been caused by the underlying disease processes, 45% of them appeared to be due primarily to severe dehydration. This article reviews recent literature on the subject, in the hope of providing a better understanding of the fluid and electrolyte derangements that underlie these self-perpetuating metabolic abnormalities.

*Incidence*

HHKNC usually develops in elderly people between the 5th and 7th decades of life, the mean age being 57 years. The condition has been reported in children, but it is extremely rare in that age group. Most of the patients have no previous history of diabetes mellitus, and in a significant number of them HHNKC is the first manifestation of the disease. Of those known to be diabetic, most of them have maturity-onselt disease which has been well controlled and have never had ketoacidosis.

*Clinical picture*

As its name implies, HHNKC is characterized by hyperglycaemia without ketosis, glycosuria, marked dehydration, serum hyperosmolarity and various degrees of coma. In the typical case, HHNKC is preceded by some acute illness, such as infection, myocardial infarction, cardiovascular accidents, pancreatitis, acute gastroenteritis or ingestion of drugs known to aggravate diabetes. There is the history of polydypsia, polyuria and weight loss for about a week or more. By the time the patients are seen in the hospital, almost all are clinically dehydrated and one-third are febrile and in shock. The change in mentation progresses from somnolence to frank coma, half of the patients are comatose on admission. In a small number of patients, focal or grand mal seizures occur. These seizures are generally resistant to anti-convulsants. They subside promptly on correction of the metabolic disturbances and do not recur as a rule. When hypotension, oliguria, stupor or convulsion have developed, the syndrome should be considered a medical emergency.

On physical examination, patients are noted to be severely dehydrated with fever and tachycardia. Hypotension occurs late as a reflection of dehydration. There may be abdominal pain and hyporeflexia as well as flaccidity or spasticity of the extremities. Of great importance in differential diagnosis is the absence of Kussmaul respirations and odor of acetone in the patient's breath.

These is no close relationship between hyperosmolarity and the severity of the symptoms. Some patients with blood sugar levels in the 500 - 600 mg/100 ml range feel well while others with similar plasma values may be comatose.

*Laboratory findings*

The laboratory diagnosis of HHNKC rests on:

1. the presence of 3 to 4 plus glycosuria without significant acetonuria;

2. extreme hyperglycaemia. Blood sugar level as high as 3000 mg% has been reported. The usual range is around 700 to 1200 mg%;

3. the absence of ketoacidosis.

Other laboratory abnormalities are due to dehydration and include leucocytosis, a high haematocrit due to haemoconcentration, and an apparent elevation of plasma proteins. The azotemia is out of proportion to the increase in creatinine concentration. A number of patients develop parenchymal renal damage with acute oliguric renal failure, and several have required dialysis. Metabolic acidosis is frequently observed, and may be due to renal faliure due to shock, lactic acidosis or both.

The serum sodium level is variable with an average of 141 mEq. per litre. The average calculated effective plasma osmolality is 353 milliosmoles per kg $H_2O$. Hypokalaemia is invariably present, and only rarely is there initial hyperkalaemia.

*Pathogenesis*

In HHNKC, hyperglycaemia is believed to have resulted from overactivity of the adrenals in response to an acute illness. The persistently high level of serum glucose eventually fatigues pancreatic beta cells, and plasma insulin level falls. Hyperglycaemia worsens, and osmotic diuresis ensues. Because water loss is greater than sodium loss, the end result is a state of hypertonic dehydration. The fluid lost is intracellular rather than extracellular water since the osmotically active glucose attracts water from the cells until intracellular fluid and extracellular fluid osmolality are equalized.

The loss of intracellular water may be chiefly responsible for the CNS dysfunction observed. The brain, being rigidly encased in bone, may shrink sufficiently to tear blood vessels at its dural attachments when extracellular osmotic solute obligates cellular dehydration.

It is also possible teleologically that in order to protect themselves against a lethal osmotic depletion of cell volume, cells may produce new osmotic solutes by breaking down the larger organic molecules. This inevitably has a profound effect on cellular function.

With the shift of intracellular water into the extracellular compartment, there is extracellular fluid expansion initially which may prevent hypovolaemia in the face of severe renal sodium loss. However, prolonged glycosuria eventually leads to sodium depletion since the increased urine flow rate through the kidney tubules interferes with sodium reabsorption. Total body potassium depletion occurs from the combined effects of hyperaldosteronism and increased exchange with sodium in the distal tubules. Acidosis, if present at all, is often due to lactic acidosis. It is usually relatively mild and responds to bicarbonate administration.

Several factors may be responsible for the absence of ketosis:

1. Presence of a small amount of insulin.

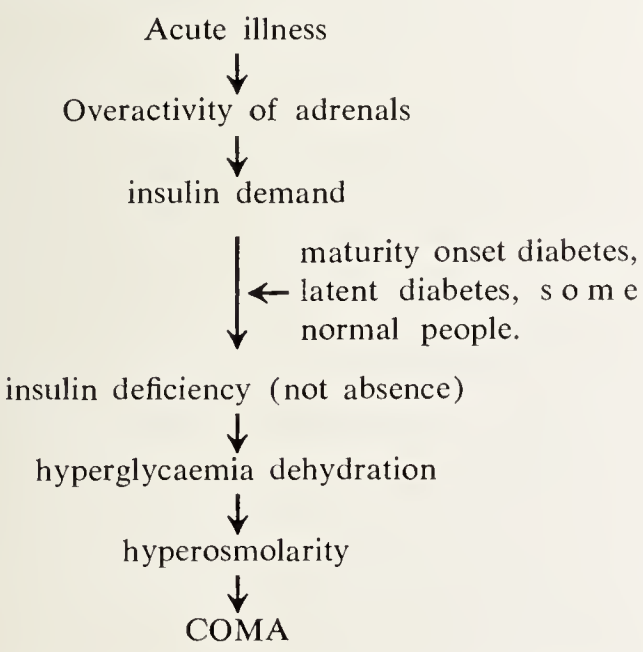
2. By increasing the deposition of glycogen in the liver, hyperglycaemia is, in effect, antiketogenic.

3. A block in the metabolic pathway of fatty acid degeneration.

4. Exogenous steroid therapy or endogenous increase in steroid production may suppress ketone body formation.

5. Dehydration may be antiketogenic.

The following scheme summaries the factors in the pathogenesis of HHNKC.




HHNKC has been reported in patients receiving glucocorticoid therapy. There is a relatively direct relationship between steroid dosage and the degree of hyperglycaemia. This condition, which improves on administering insulin and fluid, differs from hyperosmolar coma observed in elderly or latent diabetics in that large volumes of fluids are not required for the restoration of urinary output. In steroid-induced HHNKC there is no shock or insulin resistance, and upon hydration the coma does not rapidly regress, with improvement in sugar metabolism.

In the marked hyperglycaemic, non-ketonic states which may complicate dialysis or recovery from extensive burns, the condition is a result of the inability of the patient under great stress to assimilate massive glucose loads absorbed from the dialysate or intravenous fluids. Neither of these conditions indicates clinical diabetes.

*Differential diagnosis*

HHNKC must be distinguished from the following conditions.

1. *diabetic ketoacidosis*
   Ketonaemia – may reach 800 mg/100 ml.
   Plasma bicarbonate – considerably reduced.
   pH – considerably reduced.
   Osmolality – slight to moderate increase.
   Blood glucose – increased (mean approx. 700 mg/100 ml.)
   Plasma potassium – increased (mean 5.3 mEq/L).
   Plasma sodium – is usually moderately reduced.
   Leucocytosis – common even in absence of infection.
   Glycosuria and ketonuria present.
   Kussmaul breathing and odor of acetone in breath.

2. *lactic acidosis*
   Stupor or coma.
   Hyperventilation.
   Reduction in bicarbonate.
   No ketonuria or ketonaemia.
   Blood lactate exceeds 7 millimoles/litre.
   Increase in lactate: pyruvate ratio.

3. *Hypoglycaemic (insulin) coma*
   Hypoglycaemia
   Normal plasma bicarbonate.
   No ketonuria. No glycosuria provided the bladder has been recently emptied.
   Shallow or normal breathing.

4. *Other comatose states:*
   Hepatic coma, uraemic coma, cerebral vascular accidents, drug intoxication.

*Therapy*

While all recognize the importance of fluid replacement in the management of HHNKC, there is disagreement concerning what should be given in solution when intravenous therapy is initiated. Some centres advocate the use of isotonic glucose, arguing that since insulin is also given, free water will become available as the glucose is utilized. Isotonic saline, on the other hand, tends to slow down the fall in plasma osmalality. Those who use normal saline early in treatment realize that water

must be made available quickly but they want to avoid the danger of hemolysis from hypotonic solutions. They point out that episodes of shock, hypotension and sudden death have been observed following the administration of glucose in HHNKC. In addition, glucose infusion increases osmotic diuresis and hence dehydration before insulin activity increases the utilization of glucose. A third group of clinicians employ hypotonic solutions, in an attempt to overcome these various objections.

The outline of therapy suggested here is one proposed by McCurdy. According to her, fluid replacement should be conducted in three stages. In the initial stage, normal saline is infused rapidly to repair sodium deficits until blood pressure and urine flow are stabilized. Even though the patient may be severely hypertonic, hypovolemic shock is the most immediate threat to life, and hypotonic saline may not repair sodium and extracellular volume deficits fast enough to avert irreversible damage. If oliguria persists after sodium replacement, diuretics such as ethacrynic acid or furosemide may be tried. Once the sodium deficits have been corrected, 0.25 to 0.5.N saline with 10 to 30 mEq/litre of K may be used to replace urine loss during treatment.

Since the danger of water intoxication from overzealous treatment is always present, fluid replacement should be guided by the effective plasma osmolality calculated thus:

$$\text{effective } P\underset{osm}{\text{——}} = 2[Na + K] + \frac{\text{blood sugar (mg \%)}}{18} + \frac{\text{BUN (mg \%)}}{2.8}$$

In actual practice, $P\underset{osm}{\text{——}}$ can be obtained within minutes by the use of an osmomoter.

When effective plasma osmolility has confirmed that the body fluid are hypertonic, hypotonic fluids are indicated. Hypotonic saline is the fluid of choice. If oliguria is present or signs of sodium excess are present, then water can be administered as fructose or dextrose solutions.

When effective plasma osmolality approaches 325, fluid can be given orally. By this time, insulin would control hyperglycaemia and glycosuria. In other words, normal renal function can be counted upon to assist in correcting residual abnormalities in total body sodium and water.

A rough estimate of pure water deficits can be made by using clinical assessment of total body water deficits, the effective plasma osmolality and the volume of water required to reduce the osmotic concentration to a safer hypertonic level. McCurdy used the example of a severely dehydrated patient weighing 60 kg. with an effective plasma osmolality of 395 and a total body water of 30 litres. The volume of pure water needed to reduce effective plasma osmolality from 395 to 325 in his 30 litres of total body water would be 6.5 litres (by simple ratio).

Concentration of potassium in infused solutions should depend primarily on serum levels. Hypokalaemia in the presence of acidosis indicates a need to infuse potassium at higher concentrations than the usual 10 mEq. per litre.

The volume of fluid required varies from patient to patient depending on his degree of dehydration. In all but one of the reported cases, at least 5 litres were given in the first 12 hours.

Insulin plays a less important role here than in the therapy of diabetic ketoacidosis. Before sodium deficits have been replaced, hyperglycaemia is responsible for maintaining most of the plasma osmolality and hence plasma volume. Too large a dose of insulin given too rapidly may result in hyperglycaemia and hypovolemic shock. Indeed, in the 32 patients reported by Arieff and Carroll, 6 patients not hypotensive on admission went into shock as blood glucose levels fell, and 5 others became oliguric without overt systemic hypotension. The data available at present indicates that the maximum initial dose of insulin in treating HHNKC should not exceed 50 units or the hourly dose of 25 units until blood pressure is stable. If glucose level remains high a larger dose of insulin could be given after sodium deficits have been corrected. So far, the usual patient has required less than 400 units of insulin in the first 24 hours, even with glucose infusion.

If, as speculated above, idiogenic osmoles are produced as a defense against intracellular fluid depletion, rapid correction of blood glucose concentration and hypotonic fluid replacement may reverse the osmotic gradient and lead to cellular hydration. Therefore, in the third phase of treatment, insulin and fluid replacement should be guided by the falling effective plasma osmolality. Below 325, therapy should be discontinued immedaitely. If lumbar puncture reveals a high CSF pressure, intracellular oedema must be treated with hypertonic mannitol or saline. Steroids are not indicated in this situation since they are known to precipitate HHNKC.

*Prognosis*

With adequate therapy, most diabetic patients will eventually return to their previous state of control. In non-diabetics, usually no insulin therapy is required after the acute episode.

## CASE PRESENTATION

The following case serves to illustrate some of the features of HHNKC already discussed and additional points to keep in mind when confronted with the syndrome.

Mrs. L. P., an 80-year-old female, was admitted to Toronto General Hospital on July 31, 1970, with a his-

tory of vomiting, frequent urination and mental deterioration for 1 week. She was a known diabetic for 25 years and was maintained on 35 units of Lente insulin per day. She had 2 previous hospital admissions for diabetic ketoacidosis in January and February of 1969. During the February admission, EKG showed a possible posterior infarct and first degree block.

Other past illnesses included a vague story of "large" heart for over 10 years, breast cancer 8 years prior to admission, uterine growth 8 to 10 years prior to admission and a recent attack of "cystitis".

Physical examination on admission revealed a pale-looking, incoherent lady who showed signs of dehydration — dry mouth and loss of tissue turgor. Her pulse was 120/min. and regular, the blood pressure was 90/75. There was no ankle oedema or jugular venous distention. On auscultation, an $S_4$ gallop was heard. The respiratory rate was 24/min. Over the chest, there was good air entry bilaterally with moist basal rales. There was tenderness over the lower abdomen but this disappeared after voiding.

The immediate laboratory findings were:

Blood – glucose 963 mg %, Na 138, K 7.2, Cl 89, $HCO_3$, 28. (all mEq/L).
Urine – glucose 4+, acetone moderate, sp. gr. 1.026.

The patient was given 1 litre of normal saline over the next 4 hours. The initial dose of regular insulin was 20 units s.c. and 20 units i.v. At the end of 4 hours, the blood sugar had dropped to 735, K 4.5, pH 7.41 and $pCO_2$ 36. Another litre of normal saline was administered in the next 10 hours with 20 mEq. of K. She was catheterized and had a urinary output of 1250 c.c. over the next 12 hours.

17 hours after admission, the laboratory findings were:

Blood – glucose 336, Na 149, K 4.6, Cl 105, $HCO_3$ 29. BUN 8.4.
Urine – glucose 3%, acetone neg.

In view of the hypernatraemia, 350 c.c. of ½ normal saline and 1250 c.c. of D/W were given at a rate of 1000 cc/8 hours. Blood sugar level continued to drop and urine was consistently negative for acetone. The patient was digitalized.

Over the next 8 hours, urine output fell to 259 c.c. Diuresis was induced by the infusion of 4,000 c.c. of 5% D/W and in the following 15 hours, urinary output went up to 1602 c.c. Na stood at 138. 2/3 and 1/3 solution was started at 50 c.c./hour. The patient's condition remained satisfactory until August 3, the third day after admission when she suddenly turned grey, severely dyspneic, her eyes rolled up and no pulse or blood pressure was obtained. EKG showed ventricular asystole. Laboratory findings at the time were:

Blood – glucose 372, BUN 8, $HCO_3$ 23.5, pH 7.18, and $pCO_2$ 38.

The patient was transferred to the coronary unit for further management. Up to this time, she had received a total of 120 units regular insulin and 85 units of Lente insulin over 65 hours.

One hour later, the blood sugar was 580. 300 c.c. of 5% $HCO_3$ and 500 c.c. dextran were given. The intravenous line was then kept open by a slow infusion of normal saline. 40 units of regular insulin were also given.

Over the next 3 days, the blood sugar came down to around 75. Urine was negative for acetone and only occasionally positive for glucose. A total of 40 units of regular insulin and 165 units of Lente were given from the time of cardiac arrest.

On August 7, her urine was negative for both acetone and glucose. The insulin dosage was gradually tapered from 40 units Lente/day. The patient underwent an uneventful recovery and was discharged on August 26 on Lente 20 units per day.

The patient was readmitted on August 29, 1970 with a one day history of increasing drowsiness. On examination, she was semi-comatose and tachypneic. Over the chest, rales were heard diffusely. Her pulse was 120/min. and she had bilateral 2+ ankle oedema. The clinical diagnosis at this point was pneumonia and congestive heart failure. Blood glucose level was 90, and later 120.

In spite of oxygen therapy, 30 units of regular insulin and 5% D/W infusion, the patient died without regaining consciousness 2 hours after admission.

At autopsy, the pertinent findings were atrophy of the pancrease (40 gm) and generalized atherosclerosis.

The points to note in this case are:

1. The initial clinical picture and laboratory findings were not diagnostic of HHNKC. Indeed, the relatively mild hyperglycaemia, hyperkalaemia and acetonuria pointed rather to diabetic ketoacidosis. This is a problem one will encounter time and again in diagnosing these patients who often present with a combination of symptoms.

2. Initial Plasma osmolality

$$= 2\,[138 + 7.2] + \frac{963}{18} + \frac{20}{2.8} = \underline{352 \text{ milliosmole/litre}}$$

This dropped to 323 about 17 hours after admission after the patient was given 2 litres of normal saline. A total of 3 litres of fluid were given in the first 24 hours, a value below most of the reported cases.

3. The patient responded favourably to a small dose of insulin – 20 units regular insulin s.c. and 20 units i.v. This insulin sensitiviyt is characteristic of patients

*Continued on page 28*

# CLINICOPATHOLOGICAL CONFERENCE

*G. Wolcholk*, 7T2

# *Pyrexia And Confusion In An Elderly Patient*

## CASE PRESENTATION

Mr. J. C., a 77-year-old man, was brought to the emergency department of Sunnybrook Hospital on March 13, 1969, stuporous and breathing rapidly.

Five days prior to admission he had complained to his family doctor of vague right upper quadrant abdominal pain. However he continued to manage at home caring for his invalid wife but progressively becoming very confused.

Relevant past history included mild maturity-onset diabetes controlled with diet only. There was also a vague history of high blood pressure, intention tremor, and recent exertional chest pain.

Examination on admission revealed a confused, agitated elderly man who was not pale, cyanosed, or jaundiced. His response to questions was unintelligible. Oral temperature was 39°C. Respiratory rate was 30 per minute. The chest was clear to percussion and auscultation. The heart rate was 140/minute and regular, blood pressure was 150/120. The heart was clinically enlarged, demonstrating a left ventricular heave but no murmurs or abnormal heart sounds were heard. His mouth was dry and his face flushed. There was mild right upper quadrant abdominal tenderness but no guarding or rigidity. No organomegaly or abdominal masses were palpable. The bowel sounds were normal. The urinary bladder was distended. The rectal sphincter was lax, stool was of normal colour, and the prostate was enlarged. He moved all four limbs spontaneously. Power and tone were normal. Appreciation of pin prick was normal in all areas. Deep tendon reflexes were normal. The neck was supple. Fundoscopy showed no papilledema, exudates or hemorrhages. The face was symmetrical, tongue midline, and eye movements were within normal range.

Investigations showed: moderate acetonuria, 2+ proteinuria, 3+ glucosuria, 2-3 red blood cells per high power field, and no WBC's or casts. Hemoglobin was 12 gm.% and there were 17,500 WBC's/ml., predominantly polymorphs. The arterial pH was 7.442, blood glucose was 420 mg.%. Serum electrolytes were: Na 138 mEq/1, K 4.4, Cl 95, bicarbonate 18. Chest X-ray was clear, and ECG showed sinus tachycardia with left-axis deviation and left ventricular hypertrophy.

He was treated immediately with 25 units of regular insulin intravenously and continued infusion of IV fluids, electrolytes and insulin. In the next 10 hours his temperature rose to 40°C. He was started on Ampicillin and Gentamycin. A lumbar puncture was performed disclosing an opening pressure of 90 mm. $H_2O$. The fluid was white and turbid. Microscopic examination of the CSF showed 18,000 WBC's/ml. and gram-negative rods.

Despite treatment with insulin and antibodies, the patient's clinical status continued to decline until his death 12 hours after admission.

## DIFFERENTIAL DIAGNOSIS

The patient presented with a history of mild maturity-onset diabetes, right upper quadrant tenderness for five days and inreasing confusion terminating with coma and fever. The major conditions to be considered are:

(1) Ketoacidosis
(2) Infection
(3) Hypertension

The patient was a diabetic out of control. Hypotension and confusion which accompany severe hyperglycemia and dehydration often found in old diabetics were absent. The lack of localizing or lateralizing signs indicate that his mental condition most likely did not arise from a cerebral vascular accident. Despite the hyperglycemia and ketonuria, the normal pH excludes ketoacidosis. When an elderly diabetic patient presents for the first time with coma or in the pre-comatose state, the diagnosis of hyperosmolar non-ketotic diabetic coma should be entertained. As this entity has been dealt with elsewhere in this issue, it is sufficient to say here that the moderately elevated blood glucose, acetonuria, and the low normal serum sodium all rule out hyperosmolar non-ketotic diabetic coma.

The clues suggesting infection were fever and polymorphonuclear leukocytosis which appeared late in the course of the illness. The appearance of the CSF confirmed the presence of infection.

Hypertensive encephalopathy as a cause for his confusion is ruled out by the absence of retinal hemorrhages, exudates, papilledema, headaches, nausea, vomiting and convulsions.

## CLINICAL DIAGNOSIS

The most likely disease process leading to his death was meningitis. The portal of entry of infection was not apparent.

## PATHOLOGICAL EXAMINATION

*Abdomen:* The gallbladder was distended and congested. It contained thick yellow-green fluid. There were many calculi, some small and round and dark green; some larger, irregular, and yellowish green. There was

one calculus 1 cm. x 2 cm. obstructing the neck of the gallbladder. The mucosa was irregular in thickness with a small, round, yellow superficial ulcer. The wall was 3-5 mm. thick with many small abscesses containing thick yellow pus. There were fibrous adhesions in the right upper quadrant between the inferior surface of the liver, gallbladder and the hepatic flexure of the colon. The liver was congested and showed regions of fatty degeneration. The urinary bladder was acutely inflamed. The remainder of the abdomen was within normal limits.

*Chest:* The lungs were congested and there was evidence of acute purulent bronchitis.

*Central Nervous System:* The vessels of the Circle of Willis were atherosclerotic. The brain was slightly swollen and weighed 1280 gm. The meninges were opaque and congested, and there was pus on the inferior surface of the cerebellum. The cut surfaces of the brain showed congested brain tissue and pus escaping from the lateral ventricles.

On microscopy, the wall was necrotic tissue penetrated by poly-morphonuclear leukocytes. The surrounding adipose tissue was intensely inflamed. There was fibrin on the serousal surface. The cerebellum showed inflammation with marked exudate of polymorphs. The CSF grew *E. coli*. The contents of the gallbladder were not cultured.

## DISCUSSION – INFECTION IN THE DIABETIC

It is well documented that infections appear often in diabetics and that infections interfere with adequate control of diabetes. Careful observation shows that it is the uncontrolled diabetic who is more prone to infection.

The types of infection most commonly encountered are pneumonia, pyogenic infections, urinary tract infections and gram-negative septicemias. Meningitis is not common. Often organisms of low virulence are the cause of infections in diabetics, for example, Cryptococcus and Rhizopus.

Swartz and Dodge, in their series of 207 cases of bacterial meningitis report only six with *E. coli* as the causative organism. Only one case was fatal. They found *E. coli* as the sixth most common organism to produce meningitis after *D. pneumoniae, H. influenzae, N. meningitis,* β-hemolytic Strep., and other Streptococci. Rarer organisms are found to be pathogenic in non-diabetics most often after trauma or a para-meningeal focus of infection.

The gangrenous infections of poorly vascularized extremities in diabetics are readily understood. The intrigue of infections in diabetics lies in the overall decreased ability of the poorly controlled diabetic to handle infections even when his resistance to them is not significantly lowered by vascular or other complications.

The reasons for this increased susceptibility to infection are probably many but definitely poorly understood. It has been shown that fresh defibrinated blood and fresh heparinized blood of controlled diabetics have the same phagocytic, bactericidal and bacteriostatic capacities against selected strains of bacteria as blood from normal controls.[2]

Perillie *et al* revealed a factor enabling bacteremia to become established from minimal bacterial invasions in the ketotic or acidotic patient. They found that the exudate of polymorphs in response to infection is delayed three to five hours and diminished in such patients, yet there is no such delay in well-controlled diabetics. The delay is removed by correction of the acidosis.[3] Bybee and Rogers studied washed polymorphs from well-controlled diabetics, ketotic diabetics and normal controls. They demonstrated that washed polymorphs from well controlled diabetics were able to ingest and destroy bacteria suspended in diabetic or normal sera as efficiently as polymorphs from normal control patients.[1] However polymorphs from ketoacidotic patients were able to ingest a significantly smaller number of bacteria. They showed that the defect lies in the polymorph and not in the serum, and that the defect is corrected by reversing the acidosis. They also noted that bacteria survive longer intracellularly when ingested from inflammatory exudate containing ketone bodies.

This patient illustrated many of the complications of diabetes, including the diminished ability of uncontrolled diabetics to cope with infection. As expected, the elderly patient reacts differently to a disease process. An older patient may react to a severe infection without producing the signs clinicians are accustomed to looking for. This patient had no nuchal rigidity in response to a fatal meningitis. Similarly his gangrenous gallbladder produced only vague tenderness instead of the prostrating pain one expects. Geriatric patients, like paediatric patients, should therefore be evaluated with the awareness that classical symptoms and signs may be masked or modified by the influence of age on body pathophysiology.

## BIBLIOGRAPHY

1. Bybee, J. D. and Rogers, D. E.: Phagocytic leukocyte activity in diabetes. J. Lab. Clin. Med., 64, 1. 1964.
2. Marble, A; White, H. J.; Fernand, H. J.: J. Clin. Invest., 17, 423, 1938.
3. Perille, P. E.; Nolan, J. P. and Finch, S.: Studies of the resistance to infection in diabetes mellitus: local exudative cellular response. J. Lab. & Clin. Med. 59, 1008, 1962.
4. Swartz, M. T. and Dodge, S. K.: Bacterial meningitis. NEJM, 272. 725, 779, 842, 898, 1965.
5. Warren, S.; Le Compte, P.M. and Legg, M. A.: In *The Pathology of Diabetes Mellitus,* 4th ed. Philadelphia, Lea & Febiger, 1966, Chapter, p. 167.

# MULTIPLE ROUND QUIZ

H. P. DRUTZ, B.A., M.D.
FRANK G. SOMMERS, M.D.
*Residents, Toronto General Hospital*

# *Obstetrical And Psychiatric Emergencies*

*A 25-year-old primigravida had a delayed postpartum hemorrhage (8th day) requiring curettage and 3 units of blood. On her 18th postpartum day, she again hemorrhaged requiring two additional curettages and eventually uterine packing. From admission to control of hemorrhage the patient received 8 units of whole blood, 500 c.c. frozen plasma, and 3500 ml. glucose/water and glucose/saline with 200 u. of oxytocin (20-40 u./500 ml. solution). Urinary output during this period was 600 ml. During the next 24 hrs. the patient's condition remained stable. I.V. fluids during this period totalled 4050 ml. glucose/water with 200 units pitocin. Urine output was 3475 ml.*

*Approximately 24 hours after the uterus had been packed, the patient had a grand mal seizure and remanied semi-comatose, responding only to painful stimuli. Neurological examination showed no localizing signs of an intracranial lesion.*[1]

## *Questions*

1. *The most likely diagnosis is:*
   A. idiopathic epilepsy
   B. circulatory collapse
   C. hypoxia
   D. water intoxication due to oxytocin
   E. hypertensive encephalopathy

2. *One would expect serum electrolytes to show*
   A. hypernatremia and hyperchloremia
   B. hyperkalemia
   C. hyponatremia, hypochloremia

3. *Which of the following statements about oxytocin are true?*
   A. In physiological concentrations it acts to increase myometrial contractility by altering the membrane potential of individual muscle fibres.
   B. It causes milk ejection by inducing contraction of the myoepithelial cells surrounding the alveoli and fine ducts of the mammary gland.
   C. There is negligible antidiuretic activity with oxytocin administered by single rapid injection in contrast to results obtained by continuous infusion.
   D. Oxytocin acts on the distal convoluted tubules and collecting ducts of the kidney to increase water reabsorption from the glomerular filtrate.
   E. Oxytocin is best administered as a dilute intravenous solution in set amounts with close monitoring.

4. *Cerebral edema and water intoxication are associated with:*
   A. Retention in the body of large amounts of water in excess of electrolytes.
   B. Confusion, lethargy, vomiting, convulsions, coma and may terminate in death.
   C. Proportional swelling of the astrocytes due to water intake that could lead to rupturing the cell membrane.
   D. Destruction of supraventricular nuclei.

5. *Which TWO of the following is most effective in treatment?*
   A. Immediate termination of all infusions of oxytocin and electrolyte-free dextrose/water.
   B. Complete fluid restriction.
   C. Limited use of hypertonic (5%) saline solution.
   D. Use of mannitol or other potent diuretic.

6. *A forty-year-old Italian speaking woman who is six days post cholecystectomy suddenly arises from bed, starts shouting in an excited tone, goes to the window and makes motions to jump. Your course of immediate action would be:*
   A. Drag the patient back to bed and shout her down.
   B. Ask the Nurse for restraining bind.
   C. Call the duty doctor on Psychiatry.
   D. Order Valium, 10 mgm i.m. stat. and talk gently with patient.
   E. Order Largactil 50 mgm i.m. stat. and talk gently with patient.

7. *A seventeen-year-old girl is brought into Emergency by some friends, who state she has been acting strangely since taking some "acid" a few hours earlier. On examination the patient admits to feelings of panic and claims she feels her body is just an empty shell, and the room she is in is miles long with gaping doors waiting to engulf her. Your course of action might be:*
   A. Give her a sleeping pill and send her home.
   B. Admonish her for taking drugs in the first place and let her suffer through.
   C. Remove her to a quiet room, reassure her in a calm, quiet, unhurried way, prescribe Diazepam 30 mgm p.o. then re-assess her in a few hours.
   D. Order barbiturate, bromide and salicylate levels stat and while awaiting results start an I.V.
   E. Admit at once to hospital and start a phenothiazine type drug.

8. *A 47-year-old man presents in Emergency with a dishevelled appearance, glassy eyes, shaking hands and odor of spirits on his breath. He is sweating profusely and complains of great fright, caused by seeing snakes crawling on the wall before him. In response to questions he states he likes to drink now and then but has not had a drink for a couple of days. He has not held a job during the past six months and lives alone in a room.*

   *As the physician you would:*

   A. Reassure the man there are no snakes anywhere, except in his imagination and send him home to sleep.
   B. Determine blood alcohol levels and if elevated order skullX-rays, and if these are negative call the police to arrest the man for drunkeness.
   C. Take blood, start I.V. and admit patient to hospital.
   D. Order stat SGOT and alkaline phosphatase and if these are elevated, admit patient to hospital.
   E. Give patient chloridiazepoxide 50 mg. i.m. and send patient home with return appointment to the out-patient clinic.

9. *A twenty-year-old, university student states he is losing hope for society, and is no longer interested in attending classes. In fact, over a period of two months he gradually stops attendance, discontinues seeing former friends and appears to be neglecting habits of personal hygiene. There is no history of intake of hallucinogenic drugs.*

   *As the physician hearing the above history you will:*

   A. Inform the student that everyone goes through these feelings at college one time or another.
   B. Warn him to pull himself together otherwise he might fail.
   C. Inquire as to any thoughts of harming himself.
   D. Take care not to brooch the subject of suicide lest you set off dangerous thoughts.

10. *The above university student states in response to your questions that suicide has occurred to him, and in fact, he has been avoiding use of the subway lately for fear he might jump onto the tracks. He appears relieved at having had a chance to tell you this.*

    *Now you would:*

    A. Admit the patient to hospital.
    B. Tell him to take a year off school to go to work or travel in order to find himself.
    C. Place patient on Diazepam and plan to see him in weekly psychotherapy sessions.
    D. Explore with the patient his feelings, attempt to contact parents and after comforting him send the patient home in care of the parents with suggestions that he be seen by a phychiatrist.

---

# *Answers*

1. D.

2. C.

3. All

4. A, B, C.

5. A, C.

6. E.
   This woman presents the picture of extreme agitation and depression, as manifested by the shouting and suicide attempt. The immediate action calls for a tranquilizing effect and the severity of the problem is an indication for use of a neuroleptic or phenothiazine class drug. As a general principle restraint through chemotherapy is preferable to restraint by physical means. It is important to talk to the patient through an interpreter to find out the cause of her actions and to reassure her.

7. C.
   This is a patient on a "bad trip." With these cases it is best not to assume to know what psychotomimetic drug the patient took. The history together with the symptoms indicating derealization and depersonalization demand quiet surroundings with decreased stimuli and gentle "talking down". The feelings of panic are truly terrifying to the patient and the use of Diazepam usually assures a few hours of restful sleep. Afterwards, the patient's underlying psychic status must be re-assessed with a view to determine further course of action, i.e. discharge, referral for out-patient therapy or admission to hospital for further investigation and treatment.

8. C.
   This man presents the picture of acute alcohol withdrawal or delirium tremens. This condition requires hospital admission and it ought to be remembered that it is fatal in about 3% of the cases. The aim of admission is to support the circumstances of withdrawal by vitamins and good nutrition and to evaluate and attempt to treat underlying physical and emotional problems.

9. C.
   This young man is exhibiting symptoms and signs of depression. In this situation it is most important to explore whether or not the person has thought

about suicide. If you don't ask, the patient may feel the depth of his depression is not really appreciated. Furthermore, it is important to determine if the patient has considered means of suicide, e.g., has he recently purchased a revolver?

10. A
    The patient should now be judged to be dangerous to himself and admitted without delay to hospital under suicidal precautions. He will require intensive chemo- and psychotherapy.

DISCUSSION:

In the past seven years, case reports have shown the antidiuretic effect of oxytocin with the danger of water intoxication. The clinical syndrome is apparently produced by increased intracranial pressure, due to physical swelling of the brain within the fixed volume of the skull, associated with alterations in electrolyte concentrations. The commonest indications for the use of oxytocin were incomplete abortions (8 cases), postpartum haemorrhage (6 cases), missed abortion (1 case), incompetent cervix (1 case) and induction at term (1 case). Minimum fluid volumes infused in cases with convulsion were in excess of 4000 ml., most of the fluid being electrolyte-free dextrose/water. Total oxytocin dose ranged from 40 to 500 units.

Note: Uterine packing to control severe postpartum hemorrhage is a controversial approach and this procedure is disfavoured by many clinicians.

REFERENCES

1. Bilek, W.; Dorr, P.: Water Intoxication and grand mal seizure due to oxytocin. Canad. Med. Ass. J. 103, 379 (1970).
2. Kolb, L. C.: Noye's Modern Clinical Psychiatry, 7th Edition (Saunders), 1968.

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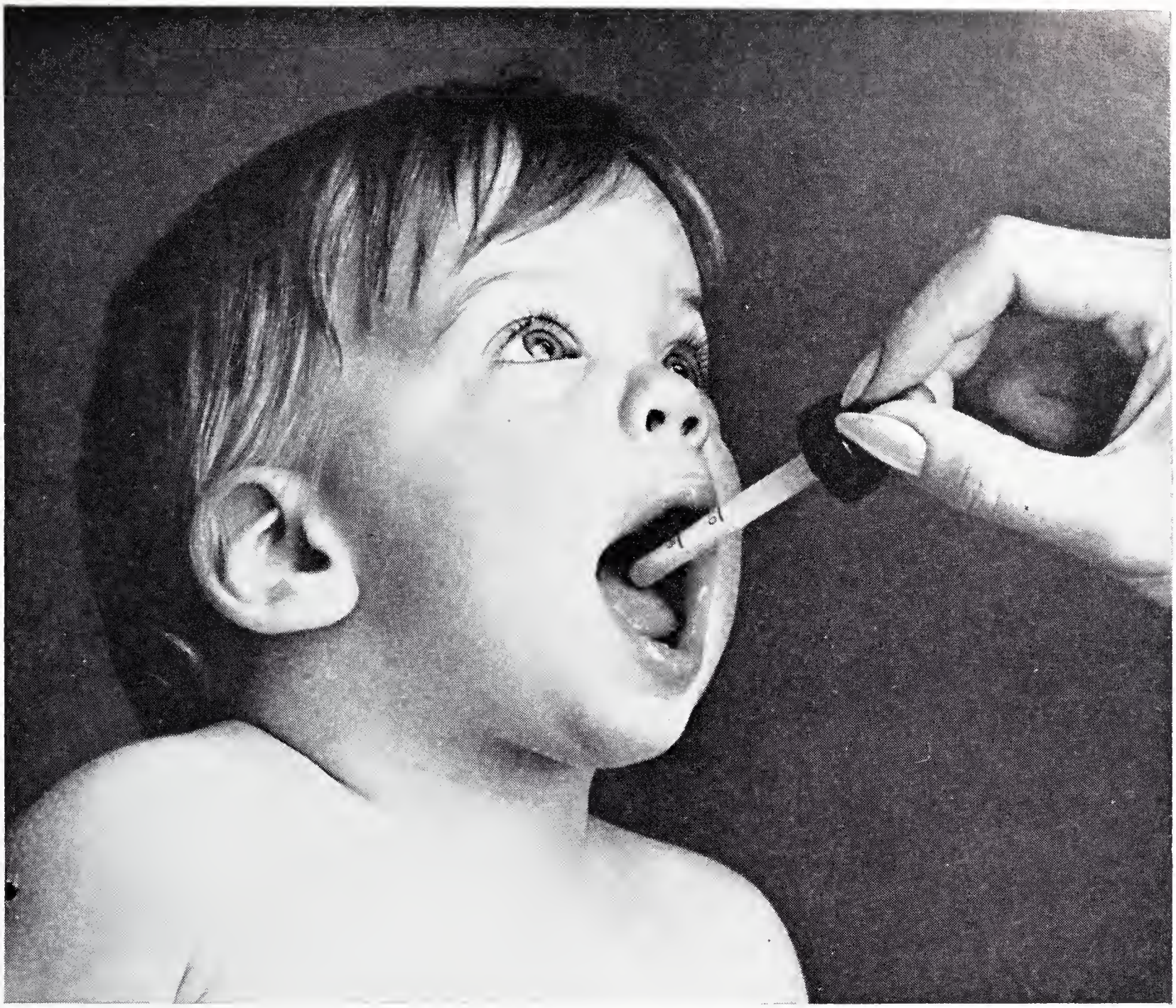
HHNKC — *Continued from page 23*

in HHNKC. Therefore, in cases presenting with signs and symptoms of both HHNKC and diabetic ketoacidosis, it is always safer to start with a small dose of insulin and to increase it if there is no sign of clinical improvement. This particular patient received only 120 units of regular insulin and 85 units of Lente insulin over the first 65 hours, in contrast to the large doses required in the treatment of ketoacidosis.

REFERENCES

1. Ashworth, C. J. et al: Hyperosmolar Coma — Its Importance In Surgical Problems, Ann. Surg. 167 : 556-60, April, 1968.
2. Boyer, M. H.: Hyperosmolar Anacidotic Coma In Association With Glucocorticoid Therapy, J.A.M.A. 202: 1007, December 1967.
3. Daniells, J. C. et al: Focal Seizures and Non-ketonic Hyperglycaemic Coma, Electroenceph. Clin. Neurophysiol. 28 : 420, April 1970.
4. Danowski, T. S. et al: Hyperosmolar and Other Types of Non-ketoacidotic Coma In Diabetes, Diabetes 14 : 164, 1965.
5. Editorial, Amer. J. Med. Vol. 45, No. 4, 485-487, October 1968.
6. Editorial, C.M.A.J., December 1968.
7. Mahon, W. A. et al: Hyperosmolar, Non-ketotic Diabetic Coma, C.M.A.J., 99 : 1090-1092, December 1968.
8. McCurdy, D. K.: Hyperosmolar Hyperglycaemic Non-ketotic Diabetic Coma, Medical Clinics of North America, Vol. 54, No. 3, May 1970.
9. Maccario, M. et al: Focal Seizures As A Manifestation of Hyperglycaemia Without Ketoacidosis, Neurology, Vol. 15, No. 3.
10. Nicholson, W. A. et al: Diabetic Coma Without Ketoacidosis, Lancet, May 2, 1964.
11. Oakes, D. D. et al: Hyperglycaemic Non-ketotic Coma In The Patient With Burns; Factors In Pathogenesis, Metabolism 18 : 103-9, February 1969.
12. Pierce, L. E. et al: Hyperglycaemic Coma Associated With Corticosteroid Therapy, New York J. Med. 69 : 1785-7, June 1969.
13. Spenney, J. C. et al: Hyperglycaemic, Hyperosmolar Non-ketoacidotic Diabetes — A Complication of Steroid and Immunosuppressive Therapy, Diabetes, Vol. 18, No. 2, 107-110, February 1969.
14. Schwartz, T. B. and Apfelbaum, R. I.: Non-ketotic Diabetic Coma, Yearbook of Endocrinology, 1965-1966, pp. 166-179. Yearbook Medical Publishers, Chicago,



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